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Symposium on Diabetes

Labile Diabetes

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Labile or brittle are adjectives used to describe diabetics who exhibit wide variations in blood glucose levels without apparent cause, and who are liable to hypoglycemia and ketosis. Many of these diabetics are thin, hyperkinetic, emotional and tense. Their diabetes is a problem to them and to their attending physicians. Understanding of some of the factors responsible for this variability may ease the task of caring for these problem patients.

The first duty of the physician is to ensure that simple errors in techniques are not responsible for this unstable stage. Even in the hospital, the physician should check the strength of insulin used in the syringe, as the administration of 80 unit insulin in a syringe designed for 40 unit strength is not uncommon. Another factor which may be responsible for variations in the effect of insulin, is the injection of the insulin into sites that have undergone lipo-atrophy or are unduly fibrosed. Simple shifting of the site of injection may correct this. Errors in timing and the amount of the diet may also contribute to lability. Before accusing the patient of cheating on his diet, the physician should review his own treatment and reserve such accusations until the patient is caught red-handed in his defections. No more certain way of destroying the patient's confidence can be devised than to accuse him of cheating when the patient knows that he is not.

Certain pathological conditions may predispose in making the patient difficult to balance. Unrecognized infections such as tuberculosis in the lungs or pyelonephritis in the kidneys may be responsible. Endocrine disturbances may contribute to the difficulty; hyperthyroidism may make diabetes very much worse; Cushing's syndrome may result in diabetes that is extremely difficult to control even with large doses of insulin.

With a loss of the pancreatic control of the release of the insulin in diabetics, the entire glucose regulating mechanism of the body is adversely affected. It is unusual to see labile diabetes in the older person who is suffering from the milder type of diabetes and whose pancreas retains some degree of function. Physical exertion has a profound effect on lowering the blood sugar. This effect is not entirely dependent on insulin and is mediated by ill-understood mechanisms. Unusual exercise in a patient who is receiving fairly large doses of insulin and who has not made appropriate adjustments in insulin or diet prior to the exercise, may precipitate hypoglycemic attacks. Such a situation is not uncommon in children and adolescents. Equally true, emotions affect glucose metabolism adversely, and emotional stress may induce marked hyperglycemia and ketosis.

The presence of ketosis has been shown to produce an increased output of adrenal cortico-steroids that may accentuate the hyperglycemia. Also, hypoglycemia will stimulate the adrenal cortex to produce more hormone and the adrenal medulla to increase the amount of circulating adrenalin. Certain of the manifestations of hypoglycemic shock, such as pallor, sweating and tremor are due to the excess circulating adrenalin. Thus, the extremes of high blood sugar and low blood sugar may activate secondary glucose regulating mechanisms that make control even more difficult.

Children with diabetes, particularly those that are showing some evidence of growth failure and undernourishment, and diabetics who are thin, may have inadequate glycogen stored throughout their bodies. This diminshed availability of glycogen may lead to profound hypoglycemia with overdosage of insulin or the rapid development of ketosis, if inadequate insulin is administered or infection supervenes.

In the relatively severe diabetic there is a continuous production of glucose from precursors during the night, despite the fact that no food is ingested. This can result in sustained elevation of the blood sugar throughout the night and early morning, and efforts to bring this fasting blood sugar to normal by the use of larger doses of a long acting insulin, such as protamine zinc, given in a single dose in the morning, may render the patient liable to severe hypoglycemia during the active periods of the day, particularly if there is any extra physical exertion. Somoygi has pointed out that doses of insulin larger than necessary may be given in attempting to achieve control, particularly when using the fasting blood sugar as a guide. This overdosage may result in severe hypoglycemia during the sleeping hours, and is unnoticed by either the patient or the observer. With the subsequent secondary release of adrenal steroids and adrenalin as compensatory mechanisms for the hypoglycemia, the blood sugar may be elevated to hyperglycemic levels by the morning. Increasing

the dose of insulin to correct the fasting blood sugar will lead to further hypoglycemic episodes with a resulting vicious circle. In most diabetics the sleeping hours are often sadly neglected in assessing the degree of control. Defective control in the blood sugar regulating mechanism has been demonstrated during these hours with unexplained variations in the blood sugar levels in the diabetic as compared to the normal.

The appearance of certain late complications of diabetes, such as nephropathy and neuropathy, may signal a period of increased "brittleness" of the diabetes. In certain patients with diabetic nephropathy the insulin requirements may be diminished, and severe hypoglycemic reaction ensue. It is interesting to speculate that, as I-131 labelled insulin is shown to concentrate in the kidney and the degradation products of insulin are excreted by the kidney, the increased insulin sensitivity in nephropathy may be due to loss of renal tissue and decreased destruction of insulin. In patients with severe diabetes mellitus who have developed a neuropathy, hypoglycemic shocks may be frequent and without warning, possibly due to lessened adrenalin output. In patients with neuropathy of the autonomic nerves of the gastro-intestinal tract, gastric atony and diabetic diarrhea with steatorrhea may result in variable absorption of food and nutritional disturbances.

When faced with the problem of these difficult diabetics, admission to hospital is almost imperative. Hospitalization will help reduce to a minimum the variables of diet, exercise, insulin and emotional problems. Every effort should be made to obtain the co-operation and understanding of the patient of the problems involved in his particular disease. Initially, a diet that has a moderate excess of calories above the minimum, should be ordered. If the patient has frequent insulin reactions it is advisable to add small lunches in the mid morning, mid afternoon and evening. Joslin suggests that some patients need small amounts of carbohydrate, e.g., salted crackers, hourly throughout the day. With the currently fashionable high carbohydrate, low fat diet, ample protein is necessary. The relatively slow transformation of a protein into carbohydrate may give them added protection against hypoglycemia.

Usually it is inadvisable to attempt to balance these patients on one dose of insulin per day. At the start, in the most severe cases, it may be necessary to give regular insulin at six-hour intervals. However, in the majority, an effort should be made to use the medium-long acting insulins, such as Lente or NPH insulin, administered before breakfast and before supper or bed time. The two dose schedule is more satisfactory than attempting to use one large dose of insulin. Rather than attempting to control the post-prandial glycosuria by increasing the dose of the medium-long acting insulins, it is advisable to add a certain proportion of regular insulin. If there is any suspicion that the patient may have been suffering from chronic overdosage of insulin, it is worth while to try slowly reducing the insulin dosage, particularly the evening dose, to a level that will allow a certain amount of glycosuria without ketosis, to ascertain if the control can be improved by this measure. Increases in insulin dosage should be made gradually rather than abruptly, because of the danger of hypoglycemia and with the resultant distress of the patient and hyperglycemic "overshoots."

All aspects of the problems associated with the diabetes must be thoroughly discussed with the patient to achieve his maximum co-operation. This frank discussion usually results in increasing the patient's confidence in his physician. The emotional problems of the patient, whether resulting from his diabetes or not, must be handled. It may be necessary to emphasize that a certain definite pattern of living, including the time and amount of meals, and the amount of exercise, is important. Before discharge from hospital, the patient should be allowed to get dressed and go out of the hospital to indulge in as normal activity as possible. It may be advisable to allow these people out of hospital showing greater glycosuria than desirable in order to compensate for extra actvities out of hospital. The final balancing should be carried on under normal living conditions, as this is the main objective.

Oral hypoglycemic agents, such as tolbutamide or chlorpropamide may be added to the regime in order to smooth out the fluctuations in the blood sugar. However, because of the nature and severity of the diabetes, it is unlikely that these drugs will suffice on their own, and the insulin will always be necessary. Because of the added hazard of a second agent, every effort should be expended to control them on insulin alone before turning to the additional oral hypoglycemic agent. Phenformin (DBI) is a more potent hypoglycemic agent, but has relatively frequent gastro-intestinal side effects. The most satisfactory results can be obtained if the patient can be encouraged to learn as much as possible about his own disease and by frequent urine testing to learn the effect of the variabilities, such as exercise and emotion. Despite all these efforts, certain patients seem to present such a difficult problem that a decision has to be made whether to exercise rigid control with the concomitant danger of hypoglycemic reactions, or to decide on a more liberal regime accepting a certain degree of glycosuria. Because of the patient's abhorrence of hypoglycemia and the likelihood of them embarking on a very free diet, it is better to accept a certain degree of glycosuria and hyperglycemia under controlled conditions.

Diabetes Mellitus in Infants and Children

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Introduction

The general principles concerned in the diagnosis and management of diabetes are common knowledge, and the details can be found in any text book of internal medicine or in the special texts devoted to diabetes mellitus. This presentation will be concerned mainly with some of the peculiar differences which diabetes presents when it occurs in the childhood age group, with emphasis upon points which are, in our opinion, not sufficiently stressed in the literature, and concluding with a sort of "Credo" which summarizes the criteriae which we believe constitute satisfactory management of the diabetic state in the child in the light of our present knowledge.

The Diagnosis

The diagnosis of diabetes mellitus in an infant or child should present no difficulty. Loss of weight in the face of adequate caloric intake, the sudden onset of frequency of urination accompanied by excessive thirst, call for prompt consideration of diabetes mellitus as the most likely diagnosis. Diabetes should also be given priority in the differential diagnosis of unexplained somnolence, coma, or dyspnoea in a child. When any of the above symptoms are combined with the finding of sugar in the urine, a blood sugar estimation should be ordered at once. The micro method should be employed where possible, especially in infants. One does not need to wait for a fasting blood sample, and there is rarely an indication for a glucose tolerance test which may actually be dangerous in the face of impending acidosis. A 1½ hour post-prandial blood sugar estimation which gives a reading of 175 mg.% or over is sufficient for diagnosis. In the presence of weight loss, thirst, polyuria or drowsiness, the reading is well likely to be over 200 mg.%, leaving no room for doubt whatever about the diagnosis.

Should a glucose tolerance test ever be done in a suspected case of diabetes mellitus? The answer is yes, but only when the random blood sugar reading is borderline and the diagnosis is in doubt. In such cases, treatment should not be commenced until a glucose tolerance test is done and all doubt resolved.

Occasionally, trace or "alimentary" glycosuria may occur and in the absence of suggestive symptoms may be ignored until further urine samples are tested. This is especially likely to occur under conditions of office practice, when a routine urinalysis on a child who has had a "treat" en route to the doctor may show a trace of sugar. In some children, an abnormally low renal threshold may result in the finding of sugar in the urine in the absence of symptoms and with a blood sugar reading well within normal limits. No treatment is required for such cases, but periodic review is advisable.

One further point needs to be stressed. The presence of sugar in the urine of the newborn infant may not signify diabetes mellitus at all. It has been shown by Haworth and others[1] that some degree of lactosuria is not uncommon in the nursery infant. It is important however to be certain that the reducing substance found in the urine is not galactose, the finding of which indicates the presence of serious metabolic disease requiring the prompt exclusion of galactose from the diet of the infant if irreparable brain and liver damage is to be prevented. It is important therefore to use test materials which will identify other sugars than glucose in the urine, especially in the newborn. The ordinary Tes-Tape is valuable mainly in mass testing and is not to be recommended for individual urinalysis in infancy.

Management

Management of diabetes mellitus in the childhood age group is beset with many difficulties which serve to set it apart from adult diabetes. The problem in childhood diabetes is, in the main, one of progressive insulin deficiency resulting finally in complete inability to produce endogenous insulin. During the first few weeks or months of the disease, however, the deficiency of endogenous insulin production may be relative only, and the initial onset of acute symptoms may be followed by apparent recovery so that insulin injections may hardly seem necessary. However, this is a temporary phase, and with the occurrence of each succeeding infection (and one may expect a child to have two or three acute infections a year) insulin deficiency becomes more marked and progressively larger doses of insulin are required to maintain satisfactory control of the diabetic state. It is important to explain the situation to the parents so that they may view the apparent rapid improvement in the diabetic child's clinical status in a realistic manner and will realize that, even though it may be possible to omit insulin for a period of several weeks or even months, its use will need to be resumed again the moment glycosuria and hyperglycemia reappear.

Insulin, diet, and exercise must each be considered in the adequate control of diabetes in the child.

Insulin

With a large variety of insulin products on the market, which should one use in the treatment of juvenile diabetes? In our experience, the rapid acting Toronto insulin is the best type of insulin to use during the first three years of life and in the first few days of the disease in any child until the dosage required to maintain control has been established. Its use is, of course, absolutely essential in the management of diabetic acidosis. The short

1. Haworth, J.: "Carbohydrate Metabolism in Children Order and Disorder." Man. Med. Review, Vol. 39, No. 7 p. 508, Aug.-Sept., 1959.

acting (4 to 6 hours) Toronto insulin is simpler to handle and is less likely to result in severe hypoglycemic reactions in the small child. When these reactions do occur, they are apt to be mild and of short duration. They are easily controlled by the administration of any carbohydrate. In contrast, hypoglycemia due to excessive long acting insulin action is much more difficult to rceognize; its effects may be prolonged and resistant to treatment. It is important to remember that the sequelae of repeated hypoglycemic reactions in infancy and childhood are serious and are much more to be feared than glycosuria or hyperglycemia. Late results of hypoglycemic reactions may present in the form of convulsive disorder, serious behaviour disturbances, and learning difficulties in the school. Hypoglycemic reactions are to be avoided at all costs.

The long acting insulins are useful in the long term management of children over three years of age. The selection should depend on the particular type of effect desired so that the maximum effect of the product will occur during periods of maximal hyperglycemia and glycosuria. N.P.H. and Lente insulins are presently favored because their maximum time of effect is between eight and sixteen hours after administration. Given in the morning, this leads to maximal effect during the late afternoon and evening hours with less action during the night when the stomach is empty. Where the problem is one of nocturnal or early morning hyperglycemia and glycosuria, protamine zinc insulin with its longer time of action (twelve to thirty-six hours) is to be preferred. One must guard, however, against hypoglycemia in the early morning hours when using this product, and remember that this may take the form not of convulsions or disordered behaviour but of difficulty in arousing the child, or in such vague symptoms as headache, mild disorientation and confusion, and difficulty in concentration in school. The diabetic child on long acting insulin who is difficult to arouse in the morning, and who is irritable and unreasonable, should have a morning blood sugar done to make sure that these symptoms are not due to too low a level of blood sugar. The actual dose of insulin is arrived at by trial and error. Since it is impossible to predict how many grams of available carbohydrate one unit of insulin will metabolize in a given patient, it is probably better to start with too little than too much. As a rough guide, one unit of insulin for every two pounds of body weight should be the maximal dose. After a few days, if glycosuria persists this dose may be increased gradually, or if control is rapidly achieved it may actually be reduced. Ideally, one should give enough insulin so that glycosuria does not exceed 15 grams in a 24 hour urine specimen, and for practical purposes this is achieved, if two out of three daily urine specimens are free of sugar. One may expect to have to increase the dose of insulin as the child grows so that where 10 units per day may suffice at two or three years of age, 20 or 30 units per day may be required by the time the child is six to eight years old.

Except for the occasional case in which a diabetic child may remain aglycosuric for a few weeks or even months after initial control of the disease, insulin is required for every childhood diabetic.

Oral antidiabetic agents have so far been of no help in the management of diabetes in the child and their use, except for research purposes, is to be condemned. Carbutamide and tolbutamide require the presence of endogenous insulin for their effect and are therefore of no use in childhood diabetes. D.B.I. has a different mode of action, probably with the liver as the main site of action, and may possibly prove to be of some value in the unstable adolescent diabetic. However, its use should not be encouraged until it is established beyond doubt that it is free of harmful effects.

One final point should be stressed. The site of insulin injection should be varied from day to day. Boggy areas, indurated areas, and areas of fat atrophy should be avoided since absorption from such sites is unpredictable.

Diet

The diabetic child's diet should be calorically adequate and should consist of the same articles of food eaten by the rest of the family. As a rough guide, it should contain 1000 calories plus 100 calories per year of age up to age 12.

At the present time, the advocates of a "free" diet appear to outnumber those favouring a measured or weighed diet. It should of course be borne in mind that the "free" diet is free only up to a point. It must be a diet containing only a moderate amount of carbohydrate and in effect implies the prohibition of candy, pie, cake, doughnuts, and the like. If these are carefully restricted, the child may be permitted unlimited fruit, vegetables, lean meat, fish, poultry, cheese, eggs, plus the usual 3 to 4 glasses of milk daily. One to two slices of bread may be offered at two meals. In a family setting where dietary habits are sensible, the "free" diet is quite satisfactory, and the child is probably protected against hypoglycemia by the urge to eat when really hungry.

Our own preference is to prescribe a measured diet, using the C.D.A. substitution lists, for a year or more until the mother becomes confident of her ability to manage her child's diabetes. Fewer changes in insulin are required, the diet may be as liberal as the "free" diet, and the family and the child develop a pattern of sensible eating habits which can then be maintained without the necessity of measuring and weighing food.

Exercise

Unless the amount of physical activity is regulated so that the diabetic child is not completelv

inactive in front of the T.V. screen one day, and playing baseball the next, satisfactory control of the child's diabetes is impossible. The child should be encouraged to take part in all activities: P.T., baseball, football, swimming, skating, biking—but should substitute some type of indoor activity on those days when because of bad weather or for other reasons outdoor activity is limited or impossible. The more sedentary the child, the more insulin will be required to maintain satisfactory control. Less insulin is required during the summer than during the school term. Difficulties in maintaining adequate control are not infrequently due to failure to pay attention to the child's day by day activities.

Criteriae of Satisfactory Diabetic Control in the Child

How does one decide whether the child with diabetes is being satisfactorily controlled? **In our opinion, this desirable state is reached when a diabetic child is able to partake of a diet that differs little from the diet of the rest of the family and receives enough insulin so that his urine is sugar free in two out of three specimens in the day, when he feels well, grows normally, attends school regularly and is able to take part in all normal physical pursuits of childhood.** For obvious reasons, horseback riding and swimming alone should not be permitted. In every other respect, the diabetic child's activities should not be restricted. Frequent admissions to hospital for "regulation of diabetes" are, as a rule, unwarranted. Regulation is much easier to achieve on an out-patient or home basis. A child lying around in a hospital bed does not present the true picture of his disease and the results of treatment in hospital cannot be compared with the response to treatment at home on normal activity.

Insulin and Diabetes

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Probably no other hormone has been as intensively studied over a period of now almost 40 years as insulin — whose failure of action is the cause of diabetes. The reason for defining diabetes as due to a failure of action of insulin rather than a lack of insulin will be discussed further in this short review.

The mechanism of action of insulin is still obscure, but its actual function has become more clearly understood in recent years due in particular to the work of Levine[1] and Stadie[2]. In the past, when considering the profound disturbances of carbohydrate, fat and protein metabolism that can occur in the diabetic state, it was convenient to think of insulin as affecting all these processes and having a number of functions. It now appears established that the majority of the metabolic disturbances associated with diabetes can be ascribed to failure in the initial stages of glucose catabolism. The other defects follow from this.

The work of Levine[1] and Park[3] conclusively demonstrated that insulin in some manner accelerates or facilitates the passage of glucose across the cell membrane. In the absence of insulin entrance of glucose into the cell is impaired and hyperglycemia follows. The phosphorylation of glucose, in which form it enters into its various reactions resulting in the production of energy, normally takes place within the cell. In the absence of insulin there is decreased entry of glucose into the cell and consequently less glucose is available for phosphorylation and ultimately, energy.

As demonstrated by Stadie[2] this important action of insulin in facilitating the entrance of glucose into the cell is associated with a rapid and firm binding of insulin by the intact cell, presumably by the cell membrane — the place at which it acts. In passing it might be mentioned that in cell-free systems of enzymes, e.g. tissue homogenates or mitochondrial preparations, insulin has no effect on the rate of glycolysis. This further supports the concept of insulin as being a factor primarily concerned with the passage of glucose from the extracellular to the intracellular environment.

Further emphasis of the importance of insulin as a factor concerned with glucose transport and not as a factor primarily affecting glucose oxidation is the demonstration that the diabetic organism has no difficulty in oxidizing fructose and deriving energy from this sugar. Insulin does not influence this process. Fructose penetrates the cell membrane readily and its permeability is not influenced by insulin. Once within the cell fructose is phosphorylated by the hexokinase reaction and undergoes glycolysis in the usual manner.

In the diabetic state, as well as a relative unavailability of glucose for oxidation, there is another obvious defect — the failure of fatty acid synthesis from carbohydrate, a defect also corrected by insulin administration. Insulin stimulates the synthesis of fatty acids from acetate, the common metabolic intermediate of carbohydrate, fat and protein metabolism, but this process has long been known to be coupled in obligatory manner with energy derived from a rapid simultaneous glycolysis. It is only comparatively recently that this process has been better understood[4, 5]. The metabolism of glucose, or rather its phosphorylated derivatives, proceeds to CO_2 and water by two pathways:

the well known Embden-Myerhof pathway with the production of reduced diphosphopyridine nucleotide (DPNH) and the hexosemonophosphate shunt with the production of reduced triphosphopyridine nucleotide (TPNH). Fatty acid synthesis requires the participation of TPNH. In the diabetic organism glucose utilization via the alternate pathway is reduced and with the resultant lack of TPNH lipogenesis ceases, despite an abundance or even an overabundance of acetate and other fatty acid precursors. Addition of insulin to both normals and to diabetics as well as stimulating glucose utilization via the Embden-Myerhof pathway stimulates glucose utilization via the hexosemonophosphate shunt and consequently increases the availability of TPNH, and thus increases lipogenesis. In the diabetic organism there is a deficiency of phosphorylated glucose resulting from the defective permeability of glucose into the cell due to insulin lack and therefore the glucose available for glycolysis is reduced; in particular the fraction of glucose utilized via the hexosemonophosphate shunt.

When fructose, a metabolizable sugar not requiring insulin in order to enter the cell is administered to a diabetic organism, utilization of this sugar via the E.M. pathway is intact but utilization via the H.M.P. shunt is still defective, and lipogenesis from fructose does not occur to any great extent in the diabetic organism[6]. This would suggest that in addition to its action at the cell membrane on glucose permeability, insulin also has some action in stimulating the enzymes concerned with the alternate pathway of glycolysis involving the generation of the TPNH necessary for fatty acid synthesis.

Diabetes, or alternatively inadequate utilization of glucose, can result from other causes than simply a lack of insulin. In such situations insulin production by the pancreas may be taking place more or less normally, but insulin antagonists or inhibitors are present in the organism. The nature of these antagonists in human diabetes is still obscure although from animal experiments one can strongly suspect the secretions of the adrenal cortex and of the anterior pituitary, particularly growth hormone[7]. Growth hormone is anti-insulin by virtue of its ability to inhibit the peripheral utilization of glucose, the rate of glycolysis by the H.M.P. shunt in particular being depressed by growth hormone. Growth hormone also appears capable of inhibiting the uptake of glucose by isolated muscle; it does not, however, interfere with the ability of insulin to bind to the cell membrane, and hence it would appear to modify or inhibit the action of insulin on glucose permeability. As well as conserving glucose from oxidation, growth hormone inhibits the oxidation of amino acids, thus facilitating conservation and growth of the protein stores. This leads to a greater dependence of the organism on fatty acid oxidation as an energy source, and in the growth hormone treated animal fatty acid oxidation can be stimulated even to the point of ketosis. The ketones plus the hyperglycemia resulting from decreased or inhibited peripheral oxidation of glucose leads to a diabetic condition.

The gluco-corticoids of the adrenal cortex, as mentioned, can also be implicated in hyperglycemic states. Excess corticoids lead to gluconeogenesis from protein due to the protein catabolic action of gluco-corticoids. However, the degree of hyperglycemia seen under such circumstances cannot be explained entirely on glucose arising from protein catabolism, for the degree of hyperglycemia observed is usually greater than can be accounted for from the amount of nitrogen excreted. A further possible implication of the adrenal cortex in diabetes can be made from the observation that the activity of glucose 6 phosphatase is stimulated by adrenal cortical hormones, thus reducing the amount of glucose available for energy. This enzyme activity is high in many diabetics and may contribute to the hyperglycemia.

Insulin as well as being implicated in carbohydrate and lipid metabolism plays a part in protein metabolism, but this action is not as well understood as in the former cases. Insulin potentiates the incorporation of amino acids into protein and conversely, the wasting of the protein stores is a well known accompaniment of insulin lack. The increased incorporation of amino acids into protein under the influence of insulin can apparently take place in the absence of added oxidizable substrate, differing in this respect from its action on the process of lipogenesis.

Another type of insulin antagonism has been reported, particularly in diabetic acidosis[8]; this appears to be an insulin antagonist of protein nature circulating in association with the alpha —1 globulin. The nature and development of this type of antagonism is not yet clearly understood. The antagonist is not a lipoprotein nor a pituitary principle, and does not seem to be related to the insulin antagonist of lipoprotein nature described by Bornstein which circulates in the blood of the depancreatized or alloxan diabetic animals. This lipoprotein insulin antagonist is presumed to be of pituitary origin because on hypophysectomy of the animal the lipoprotein insulin antagonist disappears from the circulation.

A further type of insulin antagonism occasionally met with is iatrogenic, appearing only in patients treated with beef or pork insulin. It is produced not only in diabetic patients under therapy, but occasionally in persons with more or less normal carbohydrate metabolism who are undergoing insulin shock therapy. This insulin antagonist or inhibitor in these cases is a protein associated with the gamma globulin fraction and appears to be the result of the development of anti-bodies to a foreign protein[9]. Such people though refractory to conventional insulins of beef or pork origin respond

readily to injections of human insulin. Further evidence of its anti-body nature is seen in the treatment of the condition with corticoids. There is as yet no definite evidence of development of autoimmunity to insulin. Liver tissue preparations have been shown to contain an enzyme insulinase which destroys or inactivates insulin. Whether insulinase can be invoked as a factor in the genesis of diabetes has not been established.

From this short summary it would thus appear that the problem of diabetes and insulin, though somewhat clarified in recent years, still remains a complex and confusing field, many areas of which are not yet understood. To name but one important area of darkness in the field of diabetes it is only necessary to recall that it is not known whether the complications of diabetes seen in the human, namely the development of arteriosclerosis and neuropathy, are due to the accompanying changes in the composition of blood or to fundamental changes in the metabolism of these tissues.

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A Note on Prediabetes

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Recognizable diabetes may be preceded by a very subtle metabolic disturbance barely detectable by present techniques. Surveys of diabetic families have turned up a number of people who have normal glucose tolerance under ordinary conditions, but who have abnormal glucose tolerance after the administration of a small amount of cortisone. Certain women may exhibit impaired glucose tolerance only during pregnancy and a long time later become overtly diabetic. Others may have multiple abortions or oversize foetuses years before the development of clinical diabetes. Such observations have found expression in the term "prediabetes," which has been circumspectly defined as "the state or condition of those persons who will eventually develop diabetes."[1]

A moment's reflection will suggest that "prediabetes" is etymologically unsatisfactory. The prefix properly refers to an interval of time, not to a state or condition. If an individual is normal in all respects at this moment then no state or condition exists. If he has an abnormality now then he has diabetes; there is nothing "pre" about it. It is not a new word which is needed, but an adequate definition of diabetes itself.

At the present time the single criterion for separating the diabetic individual from his fellows is the presence of a demonstrable abnormality of glucose metabolism. This criterion has arisen not through wisdom, but through technology: blood glucose levels have been very easy to measure. The glucose defect happens to be the most obvious, the most accessible, and occasionally the most acute aspect of the diabetic state. It may not be the first, the most important, or even the most specific aspect. Diabetes is a protracted disorder of the metabolism of carbohydrates, mucopolysaccharides, ground substance, lipids, and many specific tissues. The correlation between the severity of its varied manifestations is poor, and the interrelationships between them are not understood.

If we must accept the prefix, let us examine what it implies. It implies progression, from something to something: specifically, from a very mild abnormality of glucose tolerance, to hyperglycaemia, vascular disease, or some other recognized diabetic stigma. The generality of such progression is a widely-held assumption for which there is no evidence. It rests only upon two errors of logic: because the diabetic state is probably always accompanied by an abnormality of glucose tolerance, it is assumed that an abnormality of glucose tolerance is always accompanied by, or followed by, the diabetic state; because hyperglycaemia is probably always preceded by a period of deteriorating glucose tolerance, it is assumed that a mild abnormality of glucose tolerance will always deteriorate. The converse statements may be correct, but they are not demanded by logic, and they have not been proven. Without them present concepts of "prediabetes" and of "diabetes prediction tests" are untenable.

The normal limits of glucose tolerance have been defined with some precision[2-5]. If the subject is prepared with a high carbohydrate intake, is given 1.75 gm. of glucose per kg. ideal body weight by mouth, and glucose is measured by a true method, then blood glucose levels under a peak of 160, a 1½ hour value of 135, and a two hour value of 110 mg. per 100 ml. are normal, and values over 160, 140, and 120 mg. per 100 ml. respectively are abnormal [2, 3]. These are statistical facts which are not open to dispute. It is the biological significance of abnormalities, particularly minor ones, which is being questioned.

Twenty-three per cent of apparently healthy close relatives of diabetic persons have an abnormal glucose tolerance test[2]. All these subjects are

presently classified as diabetic, with all the unhappy implications pertaining thereto. In fact, no one knows what will eventually become of these people for the simple reason that **they have never been seen before.** They are perfecly healthy. They would not under ordinary circumstances be seeing a doctor, never mind having a glucose tolerance test. They have been **sought out,** because they have a diabetic relative. Their glucose tolerance test significantly exceeds the mean; therefore they are not normal, But are they diabetic?

The remaining apparently healthy relatives of diabetic subjects, who have a normal glucose tolerance test, have been given a second test after their glucose homeostatic mechanism has been stressed with cortisone[2]. Twenty-five per cent of such individuals show an abnormal result. It is suggested that these subjects are "prediabetic," that they will develop diabetes sometime in the future. No one knows. It really seems quite as likely that these minute defects of glucose disposal will in the majority of cases remain for a lifetime just the way they are.

So far, events appear to support the latter possibility. Over a period of six years very few if any subjects with mild abnormalities of glucose tolerance have shown further deterioration[6-8]. Six of 34 subjects with an abnormal cortisone glucose tolerance test have subsequently developed an abnormal glucose tolerance test[2], but none have progressed to fasting hyperglycaemia[6].

The fact remains that diabetic pedigrees do contain a high proportion of individuals with mild abnormalities of glucose tolerance. There is a possible explanation for this which no one has so far considered. These individuals may be the heterozygous carriers of the diabetic syndrome. Many mendelian recessive traits, for example sickle cell anaemia, thalassaemia, galactosaemia, phenylketonuria, are detectable in the heterozygous form by the presence of minor metabolic abnormalities qualitatively similar to those found in the fully developed homozygous form. Perhaps studies of diabetic pedigrees might be focused upon this point. They might for example concentrate upon the metabolic characteristics of the non-diabetic parents of the diabetic subject, who must both carry the trait, rather than upon his non-diabetic sibs, who will have a mixed genetic pattern. Delineation of the diabetic carrier would be a very significant advance indeed.

Finally, "prediabetes" and pregnancy: women who develop clinical diabetes in middle life, after their child-bearing years, frequently have an abnormal obstetrical history similar to that of women who actually have diabetes during their pregnancies[9-12]. As the interval between the onset of diabetes and the last conception decreases, the incidence of foetal giantism and foetal mortality increases. The cause of these phenomena is unknown, just as it is unknown when maternal diabetes is actually present. In the latter case perhaps permanent or transient hyperglycaemia resulting in foetal hyperinsulinism is the most reasonable hypothesis, but such could not occur if maternal diabetes had not yet developed. In fact, however, the foetal abnormalities have really occurred only before the maternal diabetes was diagnosed. The studies have been either retrospective or have included subjects who actually had post-prandial hyperglycaemia during pregnancy. No one has ever shown that a woman may have entirely normal carbohydrate tolerance throughout her pregnancies, produce children having the stigmata of maternal diabetes, and then herself develop diabetes at a later date. When this is demonstrated — as it may be — it will still not justify use of the term "prediabetes." It will simply prove that diabetes antedates abnormal carbohydrate metabolism.

From these reflections two practical conclusions follow. First, population surveys for diabetes based upon criteria more rigid than fasting hyperglycaemia should be discouraged. We do not know what, if anything, is wrong with the victims of these surveys, and we do not know what to do with or for them.

Second, those engaged in the practice of obstetrics should remember that an unsuccessful reproductive performance by the female may be due to the presence of mild unrecognized diabetes or something closely allied to it. It has been said that careful dietary care will diminish foetal loss by such individuals[13], and that administration of insulin, even if fasting hyperglycaemia is not present, will diminish it still further[14]. If these studies are confirmed, then such a regimen will be acceptable from the standpoint of practical therapeutics whether or not the underlying mechanism remains obscure.

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Treatment of Diabetic Coma

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The intelligent management of any metabolic abnormality must surely rest on an understanding of the fundamental changes occurring in the organism. With this understanding one can undertake a reversal of events to the extent that present knowledge permits of such a reversal. The details of the method involved in this reversal are of minor import. All that is of real importance is the principle of the therapy based on an understanding of the underlying disease process. Such an understanding will allow the physician to monitor his method from time to time to see if it is actually reversing the abnormality. Complete reversal is cure.

The management of diabetic coma falls into this category. Complete reversal is not obtained in this disease as one cannot correct completely the defect involved, which would appear to be the absolute or relative lack of insulin in the organism.

The lack of insulin leads eventually to acidosis (of a metabolic type) and coma only in certain diabetics. Coma is rare, if at all ever seen, in the elderly age onset non ketotic diabetic. On the other hand diabetic coma is fairly frequent in the growth onset ketotic type of disease and is often the presenting phenomenon in diabetes in children.

Whatever the ultimate function of insulin is, be it hexokinase activator[1], cell membrane activator[2], intracellular organizer[3], hexose monophosphate shunt stimulator[4], the end result of its lack is fai'ure of normal carbohydrate metabolism resulting in hyperglycaemia and ketosis. The hyperglycaemia will lead to an osmotic diuresis occasioned by the excess of filtered glucose — much like the artificial osmotic diuresis produced in the experimental animal by Mannitol. This diuresis depletes the organism of water and electrolyte.

Failure of carbohydrate metabolism deprives the organism of the energy of the glycolytic Myerhof's cycle (a minor source) and, more important, the energy of the Krebs Tricarboxylic aerobic cycle. Failure of function of the hexose monophosphate shunt deprives the individual of the synthesis of T.P.N.H. Triphosphopyridine Nucleotide). T.P.N.H. is a necessary substance for all synthetic processes, e.g., the synthesis of long chain fatty acids, cholesterol, protein[5]. Failure of this synthesis of fatty acid beyond the four carbon stage occasioned by T.P.N.H. lack will yield increased amounts of Beta hydroxy butyric acid and aceto acetic acid intermediates. These are also lost in the urine adding to the caloric waste which is already of a substantial degree due to the urinary loss of glucose.

The acid end products in their excretion will take with them some of the body's supply of sodium, potassium, calcium and magnesium as compensating positive ion. The breakdown of body protein to supply the energy demands of the individual and the stress imposed by this disease process, as in all disease processes, leads eventually to potassium loss in large quantities. Hence the acidosis of a diabetic is of double origin (a) acid gaining because of the increased production of acid intermediates occasioned by the failure to metabolize carbohydrate, (b) base losing acidosis in that proton (H+) acceptors are being excreted by the kidney in increased quantities.

To summarize, there is sodium and potassium loss as stated above, calorie loss in the glucose and keto acids excreted in the urine and there is a large water loss due to osmotic diuresis. All these losses stem from the failure to metabolize carbohydrate due to insulin insufficiency.

So the objectives of therapy must be as follows:

(a) To promote the metabolism of carbohydrate. For this insulin is necessary and at times carbohydrate is necessary. This will overcome the acidosis and prevent the osmotic diuresis.

(b) To recoup the water loss by giving intravenous solutions.

(c) To recoup the sodium and potassium losses.

(d) To remember that therapy can be lethal and watch for hypoglycaemic episodes, hypokalemia, hyperkalemia and water intoxication.

Now that the above objectives are understood the therapy becomes quite rational. First, the diagnosis must be absolutely established, and to do this not only the examination of the urine for sugar and ketones but the blood examination for glucose and ketones is essential. The electrolyte pattern of the plasma gives one an indication of the degree of acidosis. A means of monitoring the progress of the patient must be established and this is done by a repeated urinalysis, preferably without catheter, but often necessitating the use of catheter, and secondly repeated monitoring of the blood glucose, $C0_2$ and pH.

One must be careful in nursing a comatose patient to prevent aspiration of gastric contents in case of vomiting, and this is usually done by setting up a suction to clear the upper intestinal tract.

To promote carbohydrate metabolism insulin is mandatory and it should be fast acting, crystalline insulin given intravenously or intramuscularly or in both ways.

As in all good therapy the drug administered is remembered — the dosage should not be carried in one's head. The dosage may be obtained from recourse to standard works on diabetes and will vary from patient to patient depending upon the age and weight. In children the initial dose is approximately 2 units per kilogram of body weight for severe acidosis and subsequent doses at 2 to 3 hour intervals of ½ to 1 unit are usually appropriate[6]. The repeat doses are governed by the urinary and blood sugar findings, the urine being monitored at hourly intervals and the blood at two

hourly intervals for its sugar content. One should remember that in acidotic states inhibitors of insulin appear in the plasma, and large total doses of insulin may be required to render the individual free of ketosis which is the immediate aim of the therapy.

Along with the insulin there must be replacement of water and electrolyte, sodium especially in the early stages, and once kidney function has been demonstrated and the anabolic phase has been established by the use of insulin, potassium becomes of increasing importance.

With the excess of water being lost from the individual in the diseased state, the intravenous fluids should contain an excess amount of water. To do this hypotonic electrolyte solutions are used. They are not potassium containing in the initial stage, but later potassium is added to these solutions. 1/3 strength saline, with or without bicarbonate or lactate, makes a good intravenous starting mixture. A mixture of one part of 1/6 M. lactate, two parts of saline and five parts of water is sometimes used.

In severe acidotic states it has been suggested that intravenous 1/6 molar soda bicarbonate be given to correct the acidosis. While this may have some merit, it is largely being abandoned as the calculation of the bicarbonate necessary for the correction is invariably wrong. One cannot estimate the amount of sodium that has been lost from the extracellular to the intracellular space in states of body stress. The intravenous needs are best calculated on a basis of body surface area and the surface area as the insulin dosage should be obtained from standard charts. However, an easy calculation can be based on the fact that a 150 lb. man is 1.7 sq. metres in area, a child of 66 lbs. is 1 sq. metre and a child of 20 lbs. is ½ sq. metre in area.

In the initial therapy 3500 cc per sq. metre per day is to be given. One-half of this within the first 8 hrs. Once the urine flow is established, with the 1-2-5 mixture, and after 8 hours, the same solution plus potassium is given. There are many multi-electrolyte hypotonic solutions on the market that contain potassium. These go by many trade names and usually have a content of about 50 meq. of sodium per litre and 25 meq. of potassium. These can be used to make up the balance of the 3500 cc. per square metre remaining after the initial 8 hour infusion of the 1-2-5 mixture. As stated above, the course is monitored every two hours by blood sugars and hourly by the urine sugars. On this basis the subsequent doses of insulin are assessed and the necessity for adding glucose to the intravenous mixture is decided upon. When the blood sugar falls within the range of 250 mgm% or lower the intravenous solutions should contain glucose. This is necessary to prevent hypoglycaemia which may produce lasting effects on the brain. Once the acidosis is corrected and the patient is awake, the patient should be taken off the intravenous therapy and put on adequate diet and maintenance insulin.

Summary

In summary the essence of treatment of diabetic acidosis and coma is correction of the abnormality in carbohydrate metabolism by the use of insulin and the correction of losses of fluid and electrolyte by the use of hypotonic electrolyte solutions. The dangers in the therapy are hypoglycemia from the over ambitious use of insulin, hypokalemia from potassium lack and hyperkalemia from the intravenous use of solutions containing poatssium in the face of diminishing kidney function. To avoid these pitfalls no potassium is used until renal function is well established and to avoid hypoglycemia the intravenous solutions have glucose added to them when the blood sugar runs in the neighborhood of 250 mgm%. Using this simple set of rules the Children's Hospital of Winnipeg have recorded one death in diabetic coma in the last ten years.

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Practical Approach to the Management of Diabetes

F. Gerard Allison

Objects of treatment: To suppress symptoms and prevent complications; to restore normal weight, normal blood glucose and normal blood lipids.

Hyperglycemia has been shown to cause degenerative changes in islet cells in animal experiments. Moreover, on free diet vascular lesions are rapidly precipitated and rapidly progress. Poor control raises the percentage of retinopathy after 20 years from 3% to 31%. Giving moderate amounts of carbohydrate with appropriate insulin prevents post-prandial hyperglycemia. Proteins and vitamins should be adequate. Fats should be vegetable. The old fashioned diabetic diet full of butter, cream milk and bacon must be completely re-written. The diabetic should be on as strict a low cholesterol diet as the coronary patient.

In patients with a normal renal threshold urinalysis is a guide to adequate treatment, but in the others the best guide is a blood sugar either one hour after a meal or fasting. It is important to be aware of two fallacies of urinalysis—the acceptance of test results on old bladder urine which may be six hours out of date; and the acceptance of glycosuria as evidence against a shock when a severe shock may give enough outpouring of adrenalin to mobilize enough glycogen to cause glycosuria an hour or so after the shock. The Folin-Wu blood glucose method has been replaced in this area by a true glucose method which is 20 mg. lower than the Folin-Wu.

In severe diabetics who are difficult to balance it is necessary to use precisely calculated weighed diets, but for the great majority a simple diet is sufficient. The patient is told to eat everything at will except fats, sweets and starches. All foods containing sugar are forbidden. Diabetic jams and jellies and Sucharyl are used as substitutes. Of starches, an average diet would contain one small dish of cereal, one medium potato and five slices of bread daily.

Most fat diabetics can be controlled on diet alone. They are relatively resistant to insulin. Moreover insulin stimulates appetite and will increase the difficulty of weight reduction which is the most important therapy. Thin diabetic adults usually need insulin, and diabetic children always need it.

Insulins

Table 1

	Time In Hours		
	Onset	Peak	Termination
Toronto Insulin	1	4	10
NPH Insulin	2	9	27
Lente Insulin	2	9	27
PZI Insulin	6	22	36
Globin Insulin	1	9	21

Presented at the College of General Practice Meeting, Winnipeg, May, 1960.

Toronto insulin is used for all emergency situations. For example — severe infections, coma, pre- and post-operatively. In the pre-operative 750 ccs. of 5% glucose can be given with one quarter of the usual daily insulin. This can be continued at 6 hourly intervals until oral feeding is resumed. The most generally useful of the longer acting insulins is N.P.H. Its onset in 2 hours, peak in 9 hours and termination in 27 hours is practically identical with Lente insulin. Either N.P.H. or Lente may be mixed in the same syringe as Toronto insulin without losing the identity of the components.

When a new patient is being balanced it is advisable to have a tumbler of sweetened orange juice at the bedside and the patient briefed to watch for shock. A late protein meal may prevent nocturnal shock. Some difficult cases may require an afternoon dose of N.P.H. in addition to a morning dose to level out the valleys between shock and glycosuria. In other cases the combination of insulin and tolbutamide may smooth out the difficulty.

Table 2

	Half Life	Average Dose	Average Daily Cost	Cost Per Tablet
Tolbutamide (Orinase) (Mobenol)	5 hrs.	500 mg. tablet t.i.d.	36c	12½c
Chlorpropamide (Diabinese)	36 hrs.	250 mg. 1½ tablets once daily	19c	12c
Phenethylbiguanide (D. B. I.)	?	25 mg. tablet q.i.d.	30c	7½c

Oral Diabetic Agents

Of the oral medications for diabetes tolbutamide (Orinase or Mobenol) has a half life of five hours. Its effect is to stimulate the Beta cells of the patient's pancreas to produce more insulin. This effect is never injurious and may improve the diabetes by causing islet hyperplasia. In juvenile diabetes where the pancreatic islets no longer function this drug is useless. It has replaced insulin entirely in many of the milder cases in older diabetics—patients over 40 on less than 40 U. of insulin. The usual dose is .5 to 1.5 gm. daily in divided doses.

The other Sulfonylurea drug in common use is Chlorpropamide (Diabinese). With a half life of 36 hours this drug is given only once daily, one or two 250 mgm. tablets. It is more potent than tolbutamide but 8% of the patients have side effects, especially nausea.

In 25% of patients there may be poor results from a sulfonylurea drug—primary failure. Switching to the other sulfonylurea may be more successful. In 10% of patients on a sulfonylurea secondary failure occurs after a month or more, i.e. the patient becomes adapted to the drug and no longer responds.

A different kind oral medication has recently been offered, phenethylbiguanide, known as DBI.

Its action is not on the pancreas. By inhibiting oxidase enzymes in the Krebs cycle it increases anaerobic glycolysis. It also decreases hepatic glucogenesis. The main use of this drug is in conjunction with insulin in juvenile diabetics. It is often possible to reduce insulin dose by 60%, with smoother control[1]. Unfortunately there is a high incidence of side effects, metallic taste, vomiting, diarrhea and weakness. There are no irreversible bad effects. The dosage is 2 to 6, 25 mg. tablets daily. Average dose five tablets. If used with Sulfonylurea give one tablet t.i.d.

Complications

Ketosis is most commonly produced by neglect of insulin injection or by an infection causing leucocytosis, such as pneumonia, carbuncle, pyelonephritis, gangrene or septicaemia. The slow onset with vomiting, drowsiness, air hunger, abdominal pain and dehydration helps to distinguish ketosis clinically from insulin shock with its rapid onset of hunger, tremor, confusion and sweating. The classic case of shock can pass from normality to deep unconsciousness in a pool of sweat within half an hour, whereas, ketosis symptoms are present for many hours before unconsciousness occurs.

Treatment of ketosis involves treating the cause, the dehydration, the insulin lack. The ketotic patient with drowsiness and a B.P. over 100 may be started on 75 units of Toronto insulin subcutaneously. The unconscious patient with a low blood pressure may be given 50 units I.V. and 100 units subcutaneously initially. If the blood sugar is over 600 mg. an additional 150 units of insulin should be administered.

Another way of determining whether a massive insulin dose is necessary without waiting for a blood sugar, is to get a dark blue acetone test when acetone test powder (Denco) is moistened with plasma diluted to one part in three by normal saline[2]. After the initial loading doses insulin may be given hourly according to blood acetone tests or to fresh urine specimen preferably obtained without the infective risk of catheterization. Benedict red test 20 units, orange 16 units, yellow 12 units. Sudden onset of muscular weakness, loss of tendon reflexes and shallow respiration suggest low blood potassium which may be checked by blood chemistry or E.C.G. 20 M.Eq. of potassium may be given intravenously, or larger amounts by nasal tube in the form of 500 cc. orange juice with 2 grams of potassium phosphate added. Oliguria must be watched for and blood chemistry studied if it occurs. If blood pressure is low Dextran or Levophed may be given intravenously. This may improve oliguria.

In searching for diabetic complications we enquire for angina, claudication, neuritic pain or numbness, urinary symptoms and impotence.

On examining a diabetic we pay special attention to leg arteries, reflexes, vibration sense, pain sensation, urinary specific gravity, albumen, casts and pus, cataract, retinal haemorrhages, exudate, microaneurysms; and miniature chest plate re silent tuberculosis. Long term diabetic deterioration falls mainly on the arteries, the kidneys, the eyes and the nerves. Diabetics need more vitamins than normal people. Vitamin tablets may help to prevent neuritis. Arteriosclerotic diabetics should be warned to avoid the infected skin abrasion of the foot which may lead to gangrene. They should look after their feet the way a movie star looks after her face.

The last stage of diabetes may be illustrated by a short case history. When I was an intern in 1929, I was occasionally called to see a certain juvenile diabetic in ketosis or shock. Twenty-seven years later I was asked to see the same individual on his ultimate hospital admission. Vision had been getting progressively worse for two years because of retinopathy. His fasting blood sugar had been over 300 mgm. for some years. His blood cholesterol had fallen from 500 to 163 on a low cholesterol diet. The immediate cause of admission was frozen toes which his diabetic neuritis had not enabled him to perceive. Hypertensive heart failure plus renal oedema, plus advancing uraemia and uraemic anaemia were the problems presenting. Seventeen days later he died in uraemic coma.

Heredity and Pregnancy

The chance of inheriting diabetes varies from 100% if both parents have the disease to 9% if a first cousin is diabetic[3]. The spread of diabetes in the past has been much limited by fatal diabetic coma, by impotence and by stillbirths. Fetal loss is almost inevitable if the mother has nephropathy, calcified pelvic arteries or retinopathy[4]. Many other diabetic mothers will have live babies if the fluctuating diabetes of pregnancy is carefully controlled and if delivery occurs during the 36th week before the infant becomes too large or dies in utero from placental abnormality.

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The Kidney in Diabetes

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The first accurate account of diabetes mellitus was written in the second century A.D.[1], and the condition was probably well-recognized by physicians even before that. It is not surprising that it was originally thought to be a primary disease of the kidneys, and this view remained current until the latter half of the nineteenth century, when Von Mering and Minkowski produced diabetes in dogs by removal of the pancreas[18]. Although we now know that the kidneys are not primarily at fault, they do become secondarily involved in a very high proportion of patients with long-standing diabetes mellitus. Diabetic coma and uncontrolled infections have succumbed to the therapeutic advances of insulin, electrolyte replacement and antibiotics, and have been replaced by renal failure and cardiovascular disease as the most frequent cause of death in diabetic patients[22].

Lesions in the renal tubules, due to deposition of glycogen, were described in 1875[2], and for many years these "Armanni-Epstein" lesions were regarded by pathologists as the most valuable evidence of diabetes available at autopsy. It is interesting to speculate why it was that another sixty years elapsed before the characteristic glomerular lesions were described. Nodular diabetic glomerulosclerosis[12] — the "Kimmelstiel-Wilson lesion" — is such a striking lesion that it is difficult to believe that it would have been overlooked by the great histologists of the late nineteenth and early twentieth centuries if it had been as common then as it is now. It has been suggested elsewhere that the lesion may have been rare or non-existent prior to 1923, and that insulin and other therapeutic regimens may play some part in its production, other than by mere prolongation of life[10].

Diabetic patients are not immune to other diseases, and any renal disease may occur coincidentally with diabetes. However, there are certain conditions which are either confined to diabetics or are much more common in diabetics than in the general population. They comprise the vascular, glomerular, tubular and interstitial lesions listed below.

1. Arteriosclerosis of the renal artery and its extra-renal and intra-renal branches,
2. Arteriolosclerosis affecting both afferent and efferent arterioles,
3. Diabetic glomerulosclerosis
   (a) nodular
   (b) diffuse
   (c) exudative,
4. Deposition of glycogen, fat and mucopolysaccharides in and around the tubules.

These lesions appear to be almost inevitable consequences of longstanding diabetes. They can be recognized and differentiated by the pathologist at autopsy or during life by renal biopsy. Their clinical differentiation is always difficult and usually impossible, and at the bed side one should rest content with a diagnosis of "Diabetic Nephropathy" rather than using terms such as "intercapillary glomerulosclerosis," "Kimmelstiel-Wilson disease" etc., which have pathological implications.

5. Acute and chronic pyelonephritis,
6. Necrotizing renal papillitis.

These infective lesions are much commoner in diabetics than in the general population. Their great importance lies in the fact that they are preventable and treatable.

7. Acute renal failure,
8. Toxaemia of pregnancy.

These last two conditions are also commoner in diabetics and are included in this list for the sake of completeness. They will not be discussed further.

A detailed description of the histology of these lesions would be out of place here. Readers who are interested may consult the references at the end of this paper and the bibliographies contained therein[7, 10].

Aetiology

Most of the pathological lesions of diabetes, including the specific renal lesions, appear to be due to accumulation of lipid-protein and carbohydrate-protein complexes. Such substances are present in abnormal amounts in the blood, but whether their presence in the kidneys results from deposition from the blood stream or from local metabolic derangement is uncertain.

Equally uncertain is whether the renal (and retinal) lesions are complications of one or other of the metabolic disturbances that comprise the diabetic syndrome or whether they are concomitant changes, the inherent tendency towards which is closely allied to, though not necessarily inseparable from, the inherited tendency towards the development of diabetes itself. It has been shown that the incidence and, more especially, the rate of development of these lesions is less in patients whose diabetes is well controlled than in those who are poorly controlled, and hence it has been argued that proper control of the metabolic disturbances could eliminate them entirely[6, 9]. This argument is not completely tenable. In the first place the incidence of nephropathy, retinopathy, neuropathy and peripheral vascular disease in series of excellently controlled patients is not negligible if they survive for sufficiently long periods. Secondly, good control appears to depend upon something other than perfect co-operation between an intelligent patient and an understanding doctor. One has a strong clinical impression that some patients remain in good control and free from long-term complications despite a very lackadaisical attitude towards their treatment. On the other hand some patients who are very careful and precise about maintaining their

diet and insulin, nevertheless have frequent reactions. One cannot help but wonder whether there is some basic difference between the diseases from which such patients suffer: whether in fact the well-controlled patients may be suffering from a diabetic syndrome of different etiology from the poorly-controlled patients. This concept makes it difficult to be sure that such groups of patients are strictly comparable and that the lower incidence of complicating lesions can really be attributed to careful treatment.

Despite claims to the contrary, it seems unlikely that the specific renal lesions of diabetes have ever been produced in experimental animals. Although Lukens[14], Rich[19], Bloodworth and Hamwi[4], and others have produced renal lesions in diabetic animals, these do not, judging by their illustrations, resemble either nodular or diffuse diabetic glomerulosclerosis as it occurs in man. The lesions they found do resemble the exudative glomerular lesion seen in man, but this is not a specific lesion, and is a late manifestation of diabetic nephropathy, being found only in kidneys severely involved with the nodular and diffuse lesions.

The alleged production of diabetic renal lesions and retinal micro-aneurysms in animals treated with large doses of adrenal cortical steroid hormones[10] has led to the suggestion that over-activity of the adrenal cortex might be the mechanism of their production in man. However, no difference has been demonstrated in adrenal cortical activity in diabetic patients with and without vascular lesions[20]. Furthermore, diabetic glomerulosclerosis is not seen in Cushing's syndrome nor in patients who have been treated for some years with large doses of adrenal steroids.

Glomerulosclerosis appears to be exceedingly rare in patients with diabetes of known aetiology. Duncan[5] has reported (and illustrated) nodular glomerulosclerosis in a patient whose diabetes was apparently due to pancreatitis following mumps. We know of no reports of histologically proven glomerulosclerosis in diabetes due to pancreatectomy, acromegaly, haemochromatosis* or Cushing's syndrome. Retinal microaneurysms have occasionally been reported in patients with "acquired" diabetes, and this is of significance in view of the pathological similarities and close clinical association between the ocular and renal lesions[3].

The fact that glomerulosclerosis is so rare in "acquired" diabetes and the difficulty or impossibility of producing it in experimental animals favours the view that it is a concomitant lesion. This is, however, only circumstantial evidence: one would like to see reports of specific "diabetic" renal lesions occurring in patients with "pre-diabetes" who have not yet developed the overt metabolic abnormalities of the diabetic syndrome. No such instances have been reported.

If the concomitant theory were the correct explanation of diabetic nephropathy, one would expect its incidence to be similar in various parts of the world and at different times, but this appears not to be the case. It has already been suggested that nodular glomerulosclerosis occurred rarely or not at all prior to 1923. It appears to be uncommon in East Africa, but almost as frequent in Japan as it is in North America[10]. These facts suggest that difference in diet and other treatment may play an important part in producing the complications, and even tend to incriminate insulin, since the Japanese resemble the East Africans in the nature of their diet, but the Americans in that insulin is available to them. It has been demonstrated experimentally that insulin affects the metabolism of acid mucopolysaccharides[21] and it is a substance of this nature that is thought to be deposited throughout the body in complicated diabetes.

The weight of evidence seems to support the view that nephropathy, retinopathy, etc. are probably complications rather than concomitants of diabetes. However, they are only reduced in incidence and not eliminated by "perfect control" as we know it today. It is possible that elimination of these complications depends upon the control of some abnormality of metabolism that is not yet recognized.

Diagnosis

There are no specific symptoms of renal involvement in diabetes, except in the later stages when the nephrotic syndrome may occur. An early symptom of most sorts of renal disease is nocturia, but the significance of this is likely to be overlooked in a patient with diabetes. Early recognition depends upon regular examination of the urine for protein, cells and casts. All of these may appear transiently in small amounts in patients in diabetic ketosis, but their persistence indicates the presence of established renal disease — either a true diabetic lesion or an infection. It has been shown elsewhere that functionally it is the diffuse type of glomerulosclerosis which is important[7, 8]. The nodular "Kimmelstiel-Wilson lesion," though of value to the pathologist trying to make a diagnosis, is probably not responsible for the clinical syndrome usually attributed to it. Thus the severity of hypertension, azotaemia, and proteinuria are a guide to the severity of diffuse glomerulosclerosis.

The most important point to decide is whether or not there is infection in the urinary tract. The consistent finding of more than five white blood cells per high-powered field in a centrifuged deposit of urine should lead to the initiation of a search for an infecting organism. Because catheterization carries the risk of introducing more infection into the bladder, cultures should be made of clean-voided mid-stream specimens. This technique.

*Since this manuscript was submitted for publication, D. Becker and M. Miller have reported a review of the autopsy material from 52 patients with haemochromatosis, 22 of whom had diabetes mellitus. Of these 22, four had diabetic glomerulosclerosis of the nodular and diffuse types, and a further three had diffuse diabetic glomerulosclerosis without nodular lesions. (New England J. Med., 263: 367, 1960.)

which has been used for many years in male patients, can be equally satisfactory in females if care is taken to clean the perineum and if the urine is plated out (preferably using a quantitative technique) very soon after collection, before contaminating organisms have had time to multiply[17]. It has been shown that organisms genuinely infecting the urinary tract are likely to be present in a concentration exceeding 10,000 per c.c. in urine that has accumulated in the bladder for several hours[11].

Prophylaxis

In the absence of a clear understanding of the aetiology and pathogenesis of diabetic nephropathy, prophylaxis is at best a hit-and-miss affair. The effects of any particular regimen can only become apparent after many years, and even then they may be impossible to assess.

In general it is found that those patients whose diabetes is well controlled have a lower incidence of complications after any given period of time than those whose control is poor. This is a statistical difference applying to groups of patients. Individual patients may develop severe complications after a few years despite meticulous control, while others who are not well-controlled remain free from complications for many years. Furthermore, as has already been discussed, it is not certain that the better control and lower incidence of complications are necessarily the result of better treatment. Nevertheless, since the weight of evidence suggests that nephropathy is a complication of diabetes rather than a concomitant lesion, the initial prophylactic measure should be to ensure as near perfect control as possible for one's patients. It is important to remember that present-day assessment of "good control" depends upon the absence of hyperglycaemia and ketosis. There is no reason to think that these two substances have anything to do with the development of nephropathy. They may not accurately reflect the really important metabolic defect—whatever that may prove to be. One must, therefore, keep one's mind open to the possibility that ideal treatment for the prevention of nephropathy may be quite different from present-day regimens.

The association between degenerative arterial disease and lipid metabolism, and the effects thereon of poly-unsaturated fats, have been extensively investigated in recent years. Diabetic retinopathy and nephropathy appear to originate at the arteriolar, capillary and venular level, but nevertheless, in view of the high incidence of atherosclerosis in diabetes, it has seemed worthwhile to attempt to reduce the fat content of diabetic diets, and in particular to reduce the amount of animal, saturated fats. Kinsell and his colleagues have already gained the impression that the progress of complications has been halted by such diets[13].

Perhaps the only aspect of renal disease in diabetes in which prophylaxis can be based upon a sure footing is in the prevention of pyelonephritis. The incidence of acute and chronic pyelonephritis and urinary tract infection is considerably higher in diabetics than in the general population. The role of instrumentation of the urinary tract and indwelling catheterization in introducing infection has been repeatedly emphasized[11, 16], and they should be avoided whenever possible.

Treatment

No treatment is known which will reverse the pathological lesions of diabetic glomerulosclerosis. A few reports of the good effects of hypophysectomy have appeared, but on the whole the results of this hazardous procedure, and of adrenalectomy, have not been encouraging and at present they can be regarded only as experimental procedures.

The rational treatment of pyelonephritis depends upon isolating the infecting organism, determining its sensitivity to antibiotics, and exhibiting the appropriate drug. Relapse is common, and probably an effective antibiotic should be given for at least a month, and followed by a long-term course of a urinary antiseptic such as mandelic acid, methionine, or a sulfonamide.

Once renal failure is established, its management is similar to that of renal failure of any other aetiology. A generous fluid intake should be ensured. Protein intake should be restricted, but not below the level of "wear and tear" — 40 gm. per day, to keep pace with the kidneys' diminished ability to excrete nitrogenous waste products and fixed anions. Phosphate absorption can be reduced by aluminum hydroxide gel taken with each meal. Nausea and vomiting can be controlled with one of the numerous anti-emetic drugs now available.

Some 10% of patients with diabetic nephropathy develop the nephrotic syndrome, and present a difficult therapeutic problem. By the time the nephrotic syndrome develops there is usually marked azotaemia and it may be impossible to give the very high protein diets usually indicated in the treatment of the condition. Very prolonged and strict sodium restriction may occasionally result in diuresis and natriuretic agents such as the benzothiadiazine derivatives are of help in reducing the oedema and hypertension. In cases resistant to such measures, aldosterone-antagonists may effect a diuresis. However, they do not affect the underlying renal lesion and the protein loss which are the fundamental causes of the syndrome.

Summary

Several pathological processes affect the kidneys in diabetes mellitus. The most frequent of these are infections and the group of specific lesions referred to as "diabetic nephropathy."

The aetology of "diabetic nephropathy" is unknown, but the weight of evidence favours the view that it is a complication of diabetes itself or of present day modes of treatment. The alternative view, that it is a concomitant of diabetes, is particularly favoured by the fact that it has not yet been possible to produce the lesion in experimental

animals. This has also handicapped study of prophylaxis and treatment, which are unsatisfactory.

Instrumentation of the urinary tract probably contributes to the incidence of pyelonephritis and should be avoided whenever possible. Treatment of urinary tract infections should be based upon careful bacteriologic studies and should be continued for several months.

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Atherosclerosis of the Extremities with Special Emphasis on Patients with Diabetes Mellitus

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A high degree of association has long been recognized between atherosclerosis of the extremities (arteriosclerosis obliterans or A.S.O.) and diabetes mellitus. Among comparable groups, A.S.O. is 11 times more common in diabetic individuals[1, 2]. Atherosclerosis tends to develop at an earlier age among diabetics, but it does not differ pathologically from that found in non-diabetic individuals[2, 3]. On the other hand, among patients with peripheral vascular disease, there is a high incidence of diabetes mellitus. Bartels[4] reported that 77 per cent of patients with intermittent claudication who did not have a history of diabetes mellitus had abnormal glucose tolerance tests. Wessler[5, 6] reported that 68 per cent of subjects with acute arterial occlusion had abnormal glucose tolerance tests, and he also found that over 90 per cent of patients with arteriosclerotic gangrene have an abnormal glucose tolerance test. In a 5-year follow-up on the efficacy of lumbar sympathectomy in patients with peripheral arteriosclerosis, the incidence of amputation was three times higher in patients with diabetes mellitus and the mortality was twice as high[7]. A 40 times increase in the incidence of atherosclerotic gangrene also has been reported among patients with diabetes mellitus[1]. Thus A.S.O. is more severe both in degree and extent of involvement and in rapidity of progression among patients with abnormal glucose tolerance tests or florid diabetes.

Among patients with diabetes mellitus it is uncertain whether atherosclerosis is related to the abnormality in carbohydrate metabolism or to an abnormality in lipid metabolism. There is a definite relationship between abnormal lipid metabolism and the development of atherosclerotic lesions in patients and animals without diabetes mellitus. On the other hand there is data to suggest that the character of the control of carbohydrate metabolism has a direct bearing on the incidence of vascular involvement, apparently without regard to lipid abnormalities[8]. Regardless of the etiological relationships, the close association of diabetes mellitus and atherosclerosis should alert all physicians to periodically search for these diseases in all their patients who present with either diabetes or occlusive vascular disease.

Clinical Picture

Arteriosclerosis obliterans is asymptomatic until the reduction in blood flow is sufficiently extensive to produce ischemia. The symptoms depend on the extent and rapidity of obstruction and the ability of the collateral circulation to dilate and carry blood around the obstruction. Collaterals are preformed for the most part, but are little used in the absence of obstruction in the main vessel. With continued ischemia, collaterals dilate, hypertrophy and increase in number in a fashion tailored to the ischemic area[9]. A.S.O. predominantly involves the lower extremities, but not infrequently the upper extremities are also diseased. Subsequent remarks will refer to the lower extremities, but the principles apply to the upper limbs as well.

Intermittent claudication is the mildest degree of ischemia, i.e. ischemia on exertion only. A discom-

fort variously described as a cramp, pain, ache, weakness, or numbness is felt in a muscle group after exercise. This is related to the muscular work done and not the distance travelled. For example, a patient may walk four blocks at a slow pace but only one block at a rapid pace. The discomfort is promptly relieved by cessation of the activity without change of position. Following relief, a similar distance may again be traversed. It never occurs as a result of sitting, standing or reclining. It bears no relationship to nocturnal cramps in the legs. Depending on the proximal level of significant obstruction, the discomfort may be felt in the foot, anterior tibial muscle compartment, calf, thigh or buttock in the lower extremity. Similar areas may be involved in the upper extremity. Intermittent claudication often improves over a year or so, as the collateral circulation increases.

If the arterial supply becomes further compromised, intermittent claudication may gradually become worse. Pain may appear at rest for the first time. These changes are nearly always due to fresh thrombosis which reduces the peripheral circulation. Occasionally severe anemia may be at fault. Acute arterial occlusion is recognized clinically when this worsening in circulation is sudden and extensive, but fresh thrombus is frequently found in limbs amputated because of gangrene or pain without a clinical history of acute occlusion[5].

Rest pain is felt in the most ischemic area (the toes or forefoot) and usually is worse at night. Relief comes with walking or letting the foot hang down outside the covers. The pain may last for hours. An associated type of discomfort is termed ischemic neuropathy. Paroxysmal momentary severe shocks of pain are felt over large areas of the leg. Various types of dysesthesias are noted with these pains, the most common of which is a burning sensation, even though the foot is cold to the touch. The word neuropathy is used advisedly—no specific neuropathological changes are noted and the pains may not follow a nerve distribution. This type of pain may be long lasting and may persist even after circulation is restored. Ischemic neuropathy is more common among patients with diabetes mellitus, but in advanced diabetic neuropathy it may be absent because the limb is anesthetic[10]. The pain of ulceration and gangrene is a result of infection, rest pain and ischemic neuropathy. Peripheral hypesthesia and decreased muscular strength is often noted in the presence of severe ischemia irrespective of diabetic neuropathy. After patients have been in bed for a long time and then try to bear weight, they may have considerable pain in the feet. This is due to disuse osteoporosis and can be prevented by allowing the patient to bear weight once or twice daily during the period of bed rest.

In all patients with symptoms of peripheral arterial insufficiency there is clinical evidence of occlusive disease. No special equipment is necessary to make this diagnosis. Careful palpation of all peripheral pulses will bring any significant occlusion to light. It is important to test the compressibility (or "strength") of a pulse and compare it with its mate on the opposite side, or with a corresponding artery in the upper limb. A reduced amplitude of pulsation indicates obstruction at the point of palpation or more proximally. The proximal obstruction can be complete, as collateral circulation can transmit pulsatile flow[9]. Therefore the presence of a pulse does not exclude the possibility of a proximal obstruction. However, the systolic pressure in this collateral flow is quite low, with the result that the pulse is easily obliterated. Moreover, auscultation with a stethoscope may reveal the presence of systolic murmurs (bruits) which also indicate partial obstruction to flow. When obstruction is severe, the murmur may be continuous. Some loud murmurs are palpable as well. The following pulses are sought for in all patients with peripheral vascular disease: carotid, brachial, radial, ulnar, abdominal aorta, femoral, popliteal, dorsalis pedis and posterior tibial. Auscultation is carried out over the carotid arteries, abdominal aorta, and femoral arteries. The dorsalis pedis pulse normally is absent in about 8% of people[11]. The posterior tibial pulse is rarely absent. An artery may be palpable just distal to the lateral malleolus in these instances. If the popliteal artery is palpable, the thigh blood pressure, when compared with the blood pressure in the mate or the upper limb, will be lower in significant aorto-iliac occlusive disease. The degree of elevation pallor when the extremities are elevated for a minute or longer, and the degree of dependent rubor along with the time taken to fill superficial veins on the dorsum of the foot following elevation, are useful tests to determine the competence of the peripheral arterial system. Venous filling time is inaccurate in the presence of incompetent veins. In these situations the time taken for color to return in the toes may be substituted.

In the most severe instances of peripheral ischemia the skin of the toes and feet becomes atrophied and devoid of hair. The nails grow very slowly, if at all. Ulceration and gangrene may occur about the toes, around the nails, about calluses or at points of injury. Secondary infection is common, especially in patients with diabetes mellitus. The latter tend to have more systemic reaction than non-diabetics because the infection is more rampant in patients with the same degree of arterial disease. Oedema in the affected leg, in the absence of infection, usually indicates that rest pain is severe and the patient has been seeking relief by keeping the limb dependent.

The laboratory examination of patients with peripheral arterial occlusive disease is simple. All patients should have a glucose tolerance test to determine the presence of diabetes mellitus. A hematocrit and hemoglobin estimation help to exclude polycythemia vera. The blood cholesterol

is estimated, but a normal value does not exclude arteriosclerosis obliterans. Cardiac disease in asymptomatic patients is frequently detected by routine electrocardiography and chest roentgenograms.

Plain roentgenograms of the vascular tree are of little value in determining the presence of arterial occlusive disease. Two types of calcification may be seen. A diffuse fine calcification in the media is seen in Monckeberg's arteriosclerosis and bears no significant relationship to intimal disease. In patients with atherosclerosis there may be irregular plaques of calcium in localized segments. This does not necessarily indicate occlusive disease. On the other hand, the absence of calcification does not exclude arteriosclerosis obliterans.

Peripheral angiography will outline occlusive lesions, but is indicated in only three situations: 1) when the patient's livelihood is seriously compromised by intermittent claudication, 2) when the limb is seriously threatened by ulceration, ischemia and infection, or 3) when an aneurysm is suspected. In other words, this procedure is only indicated when corrective surgery is contemplated. Aortography has supplanted the use of selective arteriography to a large extent because unsuspected disease may be found either above or below the area of known disease, and corrective procedures carried out below an area of significant obstruction are doomed to failure. Translumbar aortography with suitable equipment safely and easily visualizes the arterial tree down to and including the vessels of the upper calf[12].

Prognosis

Arteriosclerosis obliterans is a progressive or recurrent disorder characterized by an accumulation of disseminated vascular occlusive episodes. Approximately one-third to one-half of patients 40-60 years of age, die within three years after the diagnosis of arteriosclerosis obliterans is made[10]. Death is nearly always due to a thrombotic episode in a vital organ. Moreover, repeated episodes of vascular occlusion occur which may cause great disability but not death. In a recent study of patients in whom a diagnosis of acute arterial occlusion in a leg was made after admission to a general hospital, 21 per cent died in hospital. Of those who survived, only 50 per cent could be expected to survive five years and of these, at least 25 per cent could be expected to sustain another thromboembolic episode in the legs and a similar number of thromboembolic episodes elsewhere.

The prognosis for limb survival depends on the extent and rapidity of onset of obstruction, the development of collateral circulation, recurrent thromboses, injury and infection. Ulceration and infection heal more slowly in patients with diabetes mellitus and produce more gangrene and osteomyelitis[14]. Among patients with diabetes mellitus the prognosis for limb as well as for life depends on whether the insult is produced by deficient circulation or by infection[15].

Treatment

A. A successful therapeutic regime is based on the following concepts:

1. Among patients with arteriosclerosis obliterans, the basic disorder is obstruction of the circulation due in most instances to thrombotic occlusions of atherosclerotic arteries. Direct surgery to remove or bypass this obstruction is not often applicable because of co-existing cardiovascular disease which is of greater severity. Moreover, the disease is usually widespread among patients with diabetes mellitus. The peripheral run-off in the calf is often impaired so that direct surgical procedures are less likely to succeed in these subjects.

2. The obstruction(s) to the circulation may slowly progress because of continued formation of atheromata or may suddenly worsen because of thrombosis. If the atherosclerotic process progresses slowly and the area of occlusion(s) is small, improvement in circulation and in symptoms can and does occur. A sudden change in symptomatology nearly always indicates acute thrombosis. The patient must be taught to recognize these features just as patients with coronary disease are instructed in the symptoms of "impending" myocardial infarction. Collateral circulation is tailored to the area of obstruction and tends to improve for some months after an acute episode.

3. Atherosclerosis is a disseminated disease and one must be alert for incipient disease in the coronary, cerebral, renal and mesenteric vasculature.

B. Specific Therapy:

I. Measures to arrest the progress of the disease:

Hypercholesterolemia, obesity and diabetes mellitus seem to hasten the development of atherosclerosis. Therefore dietary and other appropriate measures are indicated to control these factors. Good control of the blood sugar in patients with diabetes mellitus may not alter established atherosclerosis, but will reduce the ravages of infection.

On the basis of clinical-pathological studies it seems clear that many calamities might be prevented by the long-term administration of anticoagulants to patients with established arteriosclerosis obliterans[5, 6]. The situation in the extremities seems analogous to that in the coronary circulation, i.e., the administration of anticoagulants prevents extension and recurrence of thrombosis and facilitates fibrinolytic mechanisms, so as to encourage development of collateral circulation. However, the usefulness of anticoagulants in peripheral arterial occlusive disease awaits a statistically sound study[5]. The use of fibrinolysins is as yet uncertain in the management of acute peripheral arterial occlusion.

II. Measures to improve circulation.

1. Direct arterial surgery. With the exception of embolectomy and aneurysmectomy, direct arterial surgery in arteriosclerosis obliterans attempts to ameliorate a progressive disorder. Therefore benefits can only be temporary until the "in-flow" or "out-flow" tracts become impaired. Operation is

palliative and is indicated only when either the patient's livelihood or the survival of the limb is compromised. Careful evaluation of the cerebral, cardiac and renal vascular beds is mandatory. Preoperative peripheral angiography is carried out in nearly all instances to delineate the extent and severity of the arterial disease in the abdomen and lower extremities. The choice of the operative procedure is outside the scope of this paper. The importance of long-term anticoagulant therapy post-operatively has not yet been established.

2. Lumbar sympathetic denervation, either by surgery or by the injection of absolute alcohol, may improve the circulation to the skin in the presence of severe arterial occlusive disease. The sudomotor supply is also interrupted and this protects the skin from ulceration when hyperhydrosis, maceration and epidermophytosis are present. It is of value in alleviating mild rest pain and in the treatment of fissure ulcers and other superficial ulcerations or gangrene. There is no indication for this procedure in the treatment of intermittent claudication, acute arterial occlusion, severe ischemic neuropathy or extensive gangrene. Among diabetic patients it is mandatory to demonstrate an intact peripheral sympathetic nervous system pre-operatively, as diabetic neuropathy often involves these nerves and can produce what has been termed an "autosympathectomy." When arterial obstruction is severe, skin temperature studies are of less value than a sweating test to ascertain the presence of intact sympathetic nerves. If there is no sweating distal to mid shin it is unlikely that sympathetic denervation would be of value.

3. Drugs. A host of vasoactive drugs are now available. However, they are of questionable efficacy in the presence of severe organic occlusive disease. Alcohol is an effective vasodilating agent and in addition produces some euphoria and analgesia, and for this reason is useful in patients with disabling rest pain and in patients with acute arterial occlusion. Its use must be curtailed after the acute phase has passed, and not used at all in those with a history of alcoholism. As a corollary to this, vasoconstrictive drugs, e.g. ergot preparations, should be avoided. Tobacco in any form, with or without inhaling, produces a transient drop in peripheral skin temperature due to vasoconstriction. I do not know how often vasoconstriction has to occur in an ischemic limb before the circulation is compromised. Therefore, I usually advise complete cessation of the use of tobacco with no promises regarding symptomatic relief, but I outline these facts and leave the final decision to the patient. With the exception of the controversial disease entity, thromboangiitis obliterans (Buerger's disease), there is no absolute contraindication to the use of tobacco in peripheral vascular disease.

4. A warm environment. In our climate, exposure to cold is another very important vasoconstrictive factor. The patient with intermittent claudication must be instructed in how to avoid the vasoconstrictive effects of cold. Dressing warmly all over is most important. A car interior warmer, steering wheel muffs, fleece-lined boots, long warm winter underwear, are all useful. Wearing long socks in bed often helps a great deal in those patients who complain of an increased sensitivity to cold. In addition, when ischemia is severe as for example in acute arterial occlusion, the patient's room is maintained at a warm temperature (80 to 85° F.) and a thermostatically controlled heating box is placed over the lower legs, which are protected from the heat source. The temperature in such a box should be between 80 and 90° F. This will induce reflex vasodilatation without deleterious effects. Most patients are more comfortable with this, but a few cannot tolerate even this degree of heat without pain. Ice or alcohol sponges should never be applied except where the limb is grossly gangrenous and amputation is inevitable; and then only to reduce the absorption of toxins while preparing for amputation.

5. Mechanical means. The walking treatment of intermittent claudication has evolved from the observation that ischemia is an excellent stimulus for collateral formation. The patient is encouraged to walk to discomfort, four or five times a day. However, he is instructed to stop as soon as discomfort appears, and not wait for maximal pain before resting[9].

A slowly oscillating bed in the maximum foot-down and minimum head-down position helps to relieve rest pain and ischemic neuropathy. The patients are kept on this for a period of some eight hours a day, or even continuously. Postural exercises and other machines are of more doubtful value[16].

III. Measures used in the prevention and treatment of ulceration.

The patient with arterial occlusive disease must be cautioned about trauma and infection. He should always wear a hard soled shoe or slipper whether in the house or outdoors because of the possibility of becoming pierced by a stray pin or splinter, etc., and setting up infection. Toe nails are trimmed straight across and, if there is any difficulty in carrying this out, a well-trained chiropodist or doctor should perform this task. The use of ointments and salves containing carbolic acid, iodine, mercurochrome, and the use of medicated adhesive pads on corns, calluses, minor cuts, etc., are forbidden. These substances can easily injure the delicate skin. Direct application of heat in the form of hot water bottles and heating pads, as well as alcohol sponges and ice bags, may precipitate local gangrene. Epidermatophytosis is a common and important source of trouble. Instruction in the prevention of this condition must be thorough.

The diabetic patient with arteriosclerosis obliterans is especially prone to infection and injury

Diabetic neuropathy may involve the sudomotor fibres, resulting in a dry and atrophic skin. Fissures ulcerate easily. The daily application of cocoa butter or non-medicated lanolin will prevent this. Injury to hypesthetic areas is overlooked. Infections progress quietly and do not arouse local or systemic discomfort until far advanced. A plain roentgenogram of an ulcerated area should always be taken to determine the presence of osteomyelitis. A perforating ulcer in a callus is a classical example of this type of injury[18].

Cleansing and debridement is a most important aspect of the treatment of ulcerations. Bed rest with intermittent soaking of the ulcerated area with warm sterile solutions, (for example, saturated solutions of boric acid (4%), 0.5% aluminum subacetate, saline), and complete change of dressing 4 or 5 times a day to remove the loosened debris will nearly always succeed in cleaning up an infested necrotic area. Difficult eschars may be attacked medically by enzymatic debridement, i.e., dressings of a solution of water-miscible jelly containing streptokinase and streptodornase. Local surgical debridement is rarely necessary and should be carried out with great caution in the presence of a major arterial occlusive disease. Local application of other salves and solutions usually induces maceration which increases the size of the ulcer and delays healing. Furthermore, this increase in necrotic tissue decreases absorption of the "therapeutic agent" and therefore these ointments are usually ineffective. Infection is combatted by the systemic use of appropriate antibiotics after culture and sensitivity studies have been carried out on material taken from the ulcer discharge. Antibiotics administered systemically reach the infected area of the most ischemic ulcers; thus the local reactions of topically applied antibiotics are avoided[19]. Measures to increase local blood flow are carried out as outlined in the section above. When the ulcers are clean and the granulation tissue is healthy, the application of dry, powdered red blood cells may hasten healing. This forms a crust which is removed every 2 to 3 days by soaking with the solutions mentioned above. The use of a peripheral nerve crush or section often relieves much of the pain and allows more complete debridement in these conditions. However, unless these procedures are carried out quite proximal to the involved area, the incision made runs the risk of not healing. The application of direct arteral surgery, **where feasible**, has increased greatly the salvage of ischemic extremities.

IV. Amputation when other Measures Fail.

Amputation is indicated when gangrene extends on the leg or foot or when there is intractable pain. Pain is considered to be intractable after 6 weeks on **adequate** management. When gangrene is limited to a digit, sloughing of the gangrenous part and healing of the resulting ulcer may take place. Infection, with the exception of extensive osteomyelitis, usually responds to appropriate antibiotics if the circulation is adequate. Transmetatarsal amputations are very useful in patients with diabetes mellitus because the circulation is often better than in a non-diabetic with a similar degree of gangrene[20]. Postoperative care with muscle strengthening exercises and other physiotherapy facilitates the early use of a prosthesis. Before minor amputation is undertaken, angiography should be carried out to be absolutely sure that a potentially correctible lesion has not been overlooked. When gangrene is extensive, however, this procedure is fruitless.

Amputation is **never** an emergency. Toxemia can easily be controlled by refrigeration. Proper preoperative assessment of cardiopulmonary and renal functions as well as diabetic management is vital. Peripheral gangrene is never a threat to life[5].

Conclusions

The high degree of association between arteriosclerosis obliterans and diabetes mellitus should alert all physicians to periodically search for these diseases in all their patients who present with either diabetes or peripheral arterial occlusive disease. A conservative approach to the management of A.S.O. is predicated upon clinical-pathological studies which have demonstrated this disease to be a progressive or recurrent disorder characterized by an accumulation of disseminated vascular occlusions. Patients must be carefully instructed in meticulous foot care and the recognition of "impending" peripheral arterial occlusion. Doctors must be cognizant of the great susceptibility of ischemic tissue to injury and infection, especially among patients with diabetes mellitus. While direct arterial surgery has been a "limb-saver" to some patients, it is only a stop-gap procedure in this progressive, disseminated disorder. Indeed, most patients with severe ischemia are unsuitable for this type of surgery. Anticoagulant therapy is probably useful in "impending" and acute arterial occlusion. Long term therapy with these agents is of uncertain value. Conservation of ischemic tissues with facilitation of collateral circulation, prevention of injury and infection, and appropriate management of the diabetic state and the disturbances in lipid metabolism are the most important weapons in our therapeutic armamentarium.

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Diabetes and Pulmonary Disease

G. A. Lillington, M.D., M.S., F.R.C.P.(C)

The lung does not manifest any specific diabetic lesions comparable to diabetic retinopathy or diabetic nephropathy. Certain pulmonary diseases occur more commonly and are more severe in diabetic than in non-diabetic subjects however. Conversely, the development of pulmonary disease in the diabetic individual may aggravate the diabetic state.

The increased susceptibility of the tissues to infection in the presence of diabetes is well known. The mechanism of this vulnerability, which pertains to pulmonary tissue as well as to other body organs, is poorly understood. Most of the pulmonary "complications" of diabetes are infectious in nature.

Diabetes and Tuberculosis

Diabetics have a greatly increased susceptibility to pulmonary tuberculosis, particularly during periods of poor control or diabetic acidosis and coma. The statistical evidence for this is extensive and convincing. Older authorities spoke of "diabetic phthisis," characterized by extensive caseation necrosis, a predilection of the disease to affect midzonal and basal regions, and a greater tendency towards pulmonary hemorrhage[1]. It appears likely that these features are related more to the older age of the patient than to the presence of diabetes per se.

Since the advent of insulin, the incidence of tuberculosis in diabetics has decreased by two-thirds. Even with modern antituberculous chemotherapy however, the mortality rate from tuberculosis is twice as high in diabetics as in non-diabetics[2].

A chest x-ray should be mandatory whenever a diagnosis of diabetes is established, whether or not pulmonary symptoms are present. The onset of pulmonary symptoms in a known diabetic should be regarded with great suspicion, and appropriate diagnostic studies should be initiated.

Diabetes and Suppurative Infections of the Lung

Although statistical confirmation is scanty, clinical impressions indicate that non-tuberculous pulmonary infections have a greater incidence and increased severity in diabetic individuals as compared to non-diabetics. Suppurative pneumonia with abscess formation is particularly frequent; "diabetic gangrene of the lung" was well known to past generations of physicians[2]. In many instances, the sputum is fetid, indicating infection with a multiplicity of organisms including spirochetes and anaerobic bacteria. The prognosis is relatively good with conservative therapy, which includes antibiotics, repeated bronchoscopic aspirations and supportive measures. Vigorous treatment of minor pulmonary infections is an important prophylactic measure in diabetics.

Diabetes and Fungal Infections of the Lungs

It is probable that pulmonary mycoses of all types occur somewhat more frequently in the diabetic. In the case of mucormycosis, the relationship to diabetes is particularly striking.

Mucormycosis is a fatal fungus infection which primarily involves the cerebral blood vessels. Ophthalmoplegia and diffuse meningoencephalitis are the chief clinical manifestations, but pulmonary involvement is not infrequent. In almost all instances, diabetes mellitus is present, usually poorly controlled. Pulmonary mucormycosis is occasionally related to leukemia and multiple myeloma rather than to diabetes. No specific treatment is available.

Diabetes and Hyaline Membrane Disease

Pulmonary hyaline membrane disease is now the largest single cause of neonatal mortality; approximately one of every 400 infants dies of this syndrome[3]. It occurs with greatest frequency in premature infants, in infants born by Cesarean section and in infants born of diabetic mothers. In one series, 10 per cent of infants delivered by women with diabetes developed this disease[2].

The pathogenesis of the hyaline membrane is poorly understood. Recent studies by Lieberman indicate that there is a defect in the fibrinolytic enzyme systems in the lung in these cases[3].

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Diabetic Neuropathy

M. J. D. Newman

In an average large Diabetic Clinic about 10% of all the patients have some evidence of neurological involvement. It seems probable that a very much larger proportion of diabetics develop some form of neuropathy during the whole course of their disease. It is only fortunate that disablement is rare and many patients are quite symptom free. All varieties of neurological disease, of course, may occur in diabetics, but one form is so common and so characteristic that it certainly bears a close relation to the underlying inherited diathesis or to the metabolic disorder.

Peripheral neuropathy occurring in diabetes is somewhat unlike that found in other conditions. It involves first and most severely the sensory and autonomic nerves in the lower limbs, while motor nerves and the upper limbs are less frequently and less severely involved. Loss of sweating in the feet and loss of ankle jerks are the first signs in a slowly developing case. These are followed by diminution of pain sensation. Some spontaneous pain of variable intensity or paraesthesiae occur in some cases but by no means in all. With progression of the condition, touch and position sense become impaired in the feet, and knee jerks disappear. There may be weakness and wasting of the intrinsic muscles producing claw foot. In the severe cases, pain sensation in the feet is completely lost, perforating ulcers, and even Charcot joints may occur—the condition of Diabetic Pseudotabes. Loss of vasomotor control produces hot and dry feet, and when extensive, postural hypotension. It is only when neuropathy of the legs has reached an advanced stage that affection of the hands is seen, with sensory loss on the fingers and wasting of the small muscles.

Along with the early involvement of autonomic nerves in the leg, the sacral parasympathetic nerves are often affected. In the male, impotence is very frequent; urethral and bladder sensation may be lost causing precipitancy or retention. Diabetic diarrhea often appears to be neurogenic in origin. While sensory loss is usually more or less symmetrical, motor involvement may be markedly asymmetrical. In neither case, does the affection usually follow the distribution of individual nerves or nerve roots. In severe cases, perhaps about a third of those in which a lumbar puncture is done, the spinal fluid is abnormal, with a raised protein level.

Other types of neurological disease have been associated with diabetes but are not so common that the association can be taken as proved. Patchy spinal cord lesions are described in many of the earlier French papers on the subject, and Garland and Taverner (1953) describe a clinical picture with mixed cord lesions and peripheral neuropathy. The CSF protein was abnormal in most of these cases. Some showed improvement under a rigid diabetic regime.

Isolated cranial nerve lesions are quite commonly found in elderly diabetics. However, in this age group such cranial nerve lesions are not at all uncommon. They are usually ascribed to sclerosis and tortuosity of the carotid and other intracranial vessels.

It sometimes occurs that neuropathy typical of diabetes is found without glycosuria, but a glucose tolerance test is found to be abnormal and diabetes later develops; this is rare, but quite commonly neuropathy is the first symptom which brings the patient to a doctor or is already present when diabetes is first detected, especially in elderly patients.

Rundles (1945) in a large series from Ann Arbor pointed out that neuropathy often followed a period of neglect or heavy glycosuria. This is usually true of the more acute cases, which may come on in the course of a few weeks, but more chronic cases progressing slowly over the course of years, may develop in periods of apparently good control. Ellenberg (1960) reports cases in which neuropathy has come on paradoxically just as the diabetes was brought under control. In the young insulin-treated diabetic there is no such thing as perfect control, only degrees of bad control; but the patient with diabetes of late onset, well controlled by diet, may have permanently normal blood sugar and yet his neuropathy may still progress.

The great majority of patients with peripheral neuropathy are over 50 years of age — more than 70% according to Martin (1958). In the majority, glycosuria is persistent or regularly present. On the other hand, there is no relation to either the "severity" or the duration of the diabetes. Neuropathy is just as commonly found in cases easily controlled by diet alone as in those needing large doses of insulin. Any connection with duration of diabetes is obscured by the fact that late onset diabetes is usually present for an undetermined length of time before detection.

The exact relationship between the neurological disease and diabetes is yet to be discovered. There are three theories which could be made to harmonize with the clinical facts. First, it is possible that neuropathy is in fact congenital and is due to a factor or factors linked genetically with those causing diabetes. This would explain the apparently inexplicable onset of the condition in mild and well controlled diabetics, and its unrelenting progress in so many cases. The occurrence of typical neuropathy in a few cases secondary to acquired pancreatic disease is against such a theory. Duncan MacFarlane and Robson (1958) quote five such cases, although only one is fully described.

One of the best pathological studies in diabetic neuropathy is that of Woltman and Wilder (1929). A careful study mostly from amputated limbs

From the Abbott Clinic, Winnipeg.

showed patchy degenerative lesions with marked narrowing of the small vessels in the nerve bundles. Similar patchy lesions have been found less commonly in the spinal cord. Woltman and Wilder concluded, and many other writers have followed them, that diabetic neuropathy is due to ischemic lesions of the nerve trunks. The common symmetrical ascending character of the clinical signs would be due to summation of multiple microscopic lesions. The improvement which may occur in some cases is more difficult to explain on this theory.

If vascular disease is the cause, it is certainly a lesion of the arterioles which is responsible and not simply atheroma of the major arteries of the limb. A comparable neuropathy is not found in disease of the larger vessels, and circulation in the legs and feet is often normal even in the severest cases of neuropathy. It is possible that the small vascular lesions are analogous to these in the kidney and retinae, which simply poses the same questions of etiology over again.

Rundles from a purely clinical standpoint strongly attacked the ischemic theory and considered neuropathy to be directly due to metabolic disturbances. To some extent he was beating the air, since his arguments were directed against disease of large vessels playing a part in nerve damage, whereas if the lesion is a vasculitis of the arterioles, what is the cause of this if not metabolic? Such theorizing plays a part in directing the efforts of researchers, but we must wait for actual experimental studies to show the way in which diabetes causes neuropathy before any progress is made in treating this condition.

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The Problems of Pregnancy in Diabetes

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It is often easier to state a problem than to solve it. This paper will merely state many of the problems which arise when pregnancy and diabetes occur simultaneously. Several of these will then be singled out for fuller discussion.

The incidence of diabetes in pregnancy is generally considered to be about 1: 500 to 1: 1000. This is also approximately the incidence of diabetes in women in the reproductive age group so that diabetes, now that it is generally controlled, seems to have relatively little effect on fertility. Table 1 shows the experience at the Women's Pavilion in Winnipeg from January, 1951 through December, 1959. In a total obstetric experience of 35,716 deliveries, 61 diabetic women were delivered 81 times with 82 infants resulting. Our somewhat higher incidence than that usually reported can, I think, be readily explained by the tendency of problem cases to gravitate towards a larger center.

Figure 1

January 1951 - December 1959

Total Deliveries	35,716
Deliveries of Diabetics	81
Incidence	1:441
Diabetic Patients	61
Infants	82

Problems of Diagnosis

Let us now consider briefly the problems of diagnosis. Diagnosis of pregnancy in the diabetic woman is no different than in the non-diabetic. However, the diagnosis of diabetes during pregnancy is more difficult because:

1. In many gravidae the renal threshold is lowered and therefore glycosuria occurs without diabetes.

2. Lactosuria occurs in most pregnant women. By the usual methods of testing the amount of lactose is usually not sufficient to give a positive result until just before or after delivery.

3. There is an increased tendency to ketosis during pregnancy.

Problems Arising from the Effect of Reproduction on Diabetes

A. During Pregnancy

1. Sugar tolerance. The sugar tolerance of diabetics is apt to change during pregnancy. Usually this is in the direction of a decrease when it is thought to be due to increased activity of the anterior pituitary. Sometimes sugar tolerance is increased, ostensibly as a result of the activity of the fetal pancreas. In either event, unpredictable lability makes the diabetic more difficult to control during pregnancy. Because of the greater flexibility it permits, soluble insulin must often be used in addition to or in place of the longer acting forms.

2. Vomiting with loss of unknown amounts of carbohydrate food confuses the dietary picture and makes calculation of insulin requirements difficult.

3. Hyperemesis is much more to be feared in the diabetic because of the imminent danger of acidosis and coma. In the diabetic it is a much stronger indication for termination of pregnancy than in the normal woman.

4. The drop in renal threshold which commonly occurs in the 16 - 20th weeks makes urinalysis much less useful in assessing the need for insulin, making

more frequent blood sugar estimations necessary. It also increases the difficulties of management by leading to the loss of much larger amounts of sugar than in the nonpregnant state.

5. Increased tendency to ketosis. Pregnant women normally show an increased tendency to ketosis because of their raised B.M.R. and diminished CO_2 combining power. Therefore, when a diabetic woman becomes pregnant she becomes more prone to acidosis and coma. The ideal regime has probably not yet been discovered to avoid the opposite dangers of hypoglycemia due to insufficient calories or too much insulin on the one hand, and diabetic acidosis due to uncontrolled disease on the other. Probably a satisfactory routine, albeit a rather liberal one, is one which:

(a) achieves optimum weight gain
(b) promotes a sense of well-being
(c) keeps fasting blood sugar between 100 - 140 mg.
(d) permits glycosuria up to 10 or 15 gm. per day.

B. During Labor

1. Nutritional difficulties. It is unreasonable to expect a prescribed diet to be ingested or absorbed during labor. Therefore, it frequently becomes necessary to resort to intravenous feedings covered by soluble insulin.

2. The muscular exertion of labor may seriously deplete the liver glycogen unless adequate calories are provided.

C. During the Puerperium

1. Marked fluctuations of the blood sugar levels are apt to occur. These probably result from:

(a) changes in the physiology and metabolism as the maternal organism returns to the nonpregnant state
(b) effects of blood loss
(c) onset of lactation
(d) nervous tension and emotional instability.

Frequent urinalyses and blood sugar estimations and the use of soluble insulin for about a week are mandatory.

2. Lactosuria makes routine tests for sugar in urine much less useful.

3. Even low-grade puerperal sepsis makes the control of diabetes more difficult.

Problems Arising from the Effect of Diabetes on Reproduction

A. During Pregnancy

1. Abortion. With uncontrolled diabetes there is a high incidence of abortion and sterility. However, in the treated diabetic the rate is probably no higher than in the general population.

2. Malformations. There is a wide variation in the reported incidence of congenital abnormalities in diabetic pregnancies. An attempt has been made to attribute these to periods of hypoglycemia in early pregnancy.

3. Pyelitis. Diabetics are more prone to infections in general. Because of the relative stasis of sugar-containing urine they are particularly subject to pyelitis of pregnancy.

4. Toxemia. It is generally considered that the incidence of toxemia is about three times as great in diabetic women as in normal ones. In some it is superimposed on the degenerative vascular and renal changes commonly found in patients with diabetes of long duration. In others it is associated with overdistention of the uterine musculature.

5. Hydramnios. Gross hydramnios occurs in about 25%. This is not related to the severity of the diabetes or to the fetal or maternal blood sugar levels.

6. Feeble fetal giants. About 25% are over ten pounds. This is not related to the duration or severity of the diabetes or the blood sugar level. Over-activity of the anterior pituitary has been suggested as the cause. In practice it results in difficult prolonged labor and increases the chances of fetal injury and death. Furthermore, these large babies may not be recognized as premature and hence not receive the intensive care which they require.

7. Death in utero. Between 25 and 40% of babies of diabetic mothers die in utero, the incidence rising as term is approached. Only a few of such deaths can be explained in terms of malformations, abnormally high or low blood sugar levels, or the duration of severity of the diabetes. On the other hand there is a definite relationship between fetal death and hydramnios, toxemia, ketosis and fetal giantism. That this triad of hydramnios, toxemia and fetal giantism has the same etiology as diabetes rather than being caused by it, is suggested by the observation that they frequently occur in the pre-diabetic state. Meticulous control of the diabetes can do little to reduce this fetal loss. Such improvement as has been achieved in the past thirty years is largely due to the increasing tendency to terminate diabetic pregnancies prematurely.

B. Labor

1. Premature labor. Spontaneous prematurity is but little increased. However, induction of premature labor is common.

2. Malpresentations are common due to prematurity and hydramnios.

3. Prolapse of the cord is favored by hydramnios and malpresentations.

4. Mechanical difficulties and prolonged labor result from the over-sized babies.

5. Intrapartum deaths are common because the feeble fetal giants who have such a precarious hold on intra- or extra-uterine life stand the trauma of labor very poorly.

C. Puerperium

1. Lactation. It is probably better not to have diabetic mothers attempt to nurse their babies. Only about 50% succeed. The diabetes of a lacta-

ing woman is more difficult to control because of the additional carbohydrate metabolism required.

2. Diabetic women are more susceptible to puerperal sepsis.

When and How to Deliver the Diabetic Patient

From the standpoint of fetal salvage the interrelated problems of when and how to deliver are of the greatest practical importance. Although the use of insulin has decreased maternal mortality from up to 50% to less than 2%, the effect on fetal loss has been much less dramatic. Before insulin, Williams[1] in 1909, reported a total fetal mortality of 40%; in 1949, when insulin had been in use for about 25 years, a survey of 26 centers in Great Britain still showed a 40% loss. The best rate that I have been able to find is that of White who reported a 10% loss in 1947. Our perinatal mortality at the Pavilion from 1951 to 1960 was 18%, although the mother's diabetes was well enough controlled so that we had no maternal deaths in this series. Obviously then, control of the maternal diabetes is not the whole answer as regards fetal salvage.

These deaths may occur in utero, during labor or in the neonatal period. Many of them are sudden and have no obviously apparent cause.

Because it has been known for some time that the incidence of death in utero rises gradually from the 32nd to the 40th week it has become the practice in most centers to terminate gestation prematurely. It is this practice rather than the use of insulin which seems to be largely responsible for the recent improvement in fetal salvage. If this is indeed so, then the question as to the optimum time of delivery is of utmost importance. Statistics suggest that the risk of intrauterine death exceeds the danger of prematurity after about 36 weeks. In most centers, consequently, it has become the practice to terminate diabetic pregnancies electively at 36 or 37 weeks. Figure 2 shows that this has been the practice at the Pavilion. Those delivered earlier than this usually did so spontaneously and those

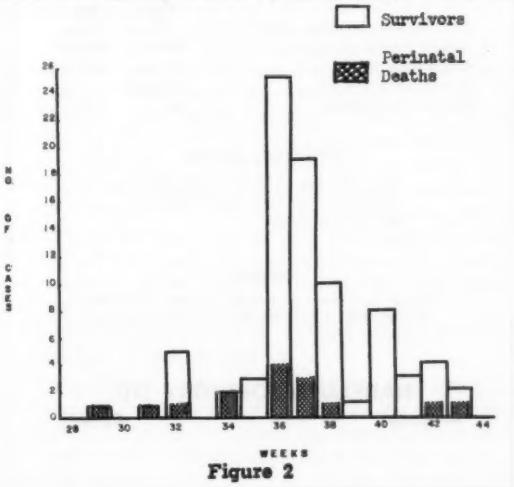

Figure 2

who went to term either had no prenatal care or were only mildly diabetic.

Of late there has been an increasing tendency to individualize rather than to terminate all cases at one arbitrary gestational age. Factors which seem to be responsible for or, at least, accompanied by intrauterine death and which are therefore taken into account when deciding at what point the specific pregnancy should be terminated include:

(a) Maternal toxemia.
(b) Hydramnios.
(c) Inability to control the diabetes, especially acidosis.
(d) A large baby.
(e) Previous intrauterine death.
(f) Decrease in fetal movement.

Depending on the appearance of these signs pregnancy may be terminated as early as 32 weeks or allowed to go to term.

No less important than the question of when to terminate pregnancy is the related one of how to do so. Most authors consulted prefer artificial rupture of the membranes to cesarean section especially in multigravidae with a soft dilatable cervix. Then some present figures which show that from the standpoint of the fetus, section gives better results. Those of Oakley and Peel[2] are typical; 20% total fetal loss in 149 patients delivered after induction as against 16% in 213 sections.

Points in favor of cesarean section over induction or even spontaneous labor include:

1. It is a certain and rapid means of delivery: fetal death may well occur in the interval between artificial rupture of the membranes and onset of labor.

2. The diabetic's fetus stands labor very poorly. Oakley and Peel say one fetus in six dies an intrapartum death in spontaneous or induced labor as opposed to 1: 70 during section.

3. Labor is likely to be desultory in onset, prolonged in duration, and difficult because of the large size of the baby.

4. Surgery and anesthesia can be planned as opposed to the emergency action which may have to be taken when fetal distress occurs during labor.

5. Maternal diabetes is easier to control through the short course of an abdominal delivery than a prolonged vaginal one.

The formidable array of arguments would seem to show conclusively that all diabetic women should be delivered abdominally, and yet most authorities advise vaginal delivery if obstetric factors seem favorable, even if, as already stated, their own figures show better results by abdominal than by vaginal delivery. This apparent inconsistency is largely due to the fact that known intrauterine deaths are almost always delivered vaginally and therefore the figures for vaginal delivery include many deaths which are in no way attributable to the method of delivery.

Figure 3

Outcome by Mode of Delivery

Gestation Under 37 Weeks

	Spontaneous	Induced	C.S.	Total
Cases	7	4	25	36
Survived	3	4	20	27
Perinatal Death	4	0	5	9
% LOST	57%	0	20%	25%

Gestation Over 37 Weeks

	Spontaneous	Induced	C.S.	Total
Cases	13	11	22	46
Survived	11	9	20	40
Perinatal Death	2	2	2	6
% LOST	15%	18%	9%	13%

Gestation All Ages

	Spontaneous	Induced	C.S.	Total
Cases	20	15	47	82
Survived	14	13	40	67
Perinatal Death	6	2	7	15
% LOST	30%	13%	15%	18%

Figure 3 shows the method of delivery and results for each at the Pavilion. Overall fetal loss at 18% compares favorably with most other series. Under 37 weeks the total fetal loss was 25%, roughly twice as great as the 13% for 37 weeks and over. By mode of delivery, cesarean resulted in 15% loss, induced vaginal delivery in 13% loss, and spontaneous vaginal delivery in 30% loss. However, if macerated fetuses are excluded the last figure comes down to 12½%, and the small differences which remain are not statistically significant. Although the figures are too small to draw definite conclusions from subgroups, they suggest that from the standpoint of the fetus we should do more inductions in the very premature ones and more cesareans in the relatively less premature ones. As hyaline membrane disease, which occurs more often after a cesarean than vaginal delivery, was a very frequent cause of death in these cases, this too suggests that it might be better to try induction in more early cases in spite of relatively unfavorable obstetric factors. In this entire series of 81 cases induction failed only once.

Summary of Management

1. Meticulous control of diabetes prevents maternal deaths.

2. Premature delivery reduces fetal loss. Time of delivery is best decided on an individual basis rather than by an arbitrary rule.

3. Vaginal delivery deserves consideration in all cases. No harm should result from a failed induction.

Acknowledgments

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LEUKORRHEA

VAGINAL INFECTIONS

CONES AND TABLETS

TWO FORMULAS

OVOQUINOL-PLAIN

	Cones	Tab.
Dilodohydroxyquinoline U.S.P.	75 mg.	75 mg.
Sodium Propionate	500 mg.	250 mg.
Sulfadiazine U.S.P.	400 mg.	400 mg.
Phenoxyethanol B.P.C.	0.04 ml.	
Destrose and Lactose	q.s.	q.s.

OVOQUINOL-OESTRO

Same formula as OVOQUINOL-PLAIN plus 0.01 mg. Ethinyl-oestradiol B.P. per cone or tablet.

DOSAGE

One or two cones or tablets per day preferably at bed-time or as prescribed by the physician.

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Address to Manitoba Medical Association

Hon. G. Johnson, M.D.

It is my privilege to bring the traditional greetings from the Provincial Government to all of you here in attendance at this 52nd annual meeting of the Manitoba Medical Association. I am sure it is most gratifying to the President and his hard-working Executive to have such a wonderful turnout of the members. May I extend a special welcome to those who have come from outside the province.

I would like to point out, Mr. President, that for the past two days there has been a reunion of an outstanding class of the Manitoba Medical School, the class of 1950. After a ten-year absence lectures were resumed at the St. Regis Hotel Saturday evening, and I believe they are still probably going on. Looking around, I am beginning to think I am one of the few survivors here today. To those who are here, I am sure the Association will bear with me when I wish this special class a hearty welcome on this their 10th Anniversary, and a very special welcome to those members who have drifted away from the province in pursuit of their careers but are back with us again today.

First of all, Mr. Chairman, I would like to take this opportunity to thank the members of the M.M.A. Executive for all their assistance and co-operation over the past year. No words can express my personal appreciation for the wonderful spirit of co-operation and understanding which the Manitoba Medical Association has shown to myself and to my Department over the past year. Your ideas have been given to us candidly, forcefully and honestly. We all realize much remains to be done, and the challenge to the profession and the government is very great. I am sure we all feel we are now entering a new era in the medical and hospital field.

Over the years every province in Canada has slowly been developing public health and welfare services in response to the increasing demands of the people. The point has been reached in most provinces, and Manitoba is no exception, where the expenditures annually on health and welfare services are the biggest single item in the provincial budget. In our own province, in the Department of Health and Welfare we will this year disburse over 40% of the total provincial expenditures in meeting the needs of Manitobans in the Health and Welfare area, 24 million dollars in the Health and Welfare Departments, and approximately 30 million dollars in hospitalization.

The activities and policies of this Department affect every man, woman and child in the province. For example, under the Manitoba Hospital Services Plan one in three Manitobans used the Plan in the first two years of its operation. These expenditures fortunately reflect not only increasing activity at governmental level, but also increased voluntary and community activity. I do not believe any other department of government deals with so many voluntary agencies, charitable institutions, local governments, professional groups and individual citizens as does the Department of Health and Public Welfare. If it were not for participation by these groups, the activities of the Department would be far less effective or meaningful. What gives meaning is that in our democratic society not only politicians and governments, but also voluntary groups, churches, professional bodies and just plain citizens are concerned about unmet needs for health and welfare services. The philosophy of government should be to co-ordinate and stimulate voluntary participation in its various activities. For example, what is the use in building a beautiful new hospital, if there is no community pride and participation in its para-medical activities? Another example, what is the use of an elderly persons housing act, which creates accommodation in co-operation with voluntary, charitable and municipal organizations, unless those organizations exist? What is the use of a room in that residence if people are placed in this accommodation without adequate professional assessment and without a program for the patient? The success of this type of accommodation depends on the many professional and voluntary organizations in the community. The support of the public who work with and for such an organization makes such a project live.

What I am trying to say is that in the field of health and public walfare, probably more than anywhere else, people want their needs met. By and large, they are willing to pay for good service if it meets that need. I know we all accept the fact that when a patient gets really sick, he expects decent accommodation and a high standard of care. Government today must give leadership, developing policies which do meet these needs in a practical and economical manner, and the policies must be so designed as to stimulate participation by all elements of society. I am sure I merely have to point to the practice of medicine under our voluntary system in the operation of hospitals by voluntary groups. I think it is basic that all of us should like to see this preserved. I think society will permit this system to continue as long as it is satisfied with the results obtained. We must on the one hand maintain a standard of care which is satisfactory, and we must keep the cost within reach of the public.

The doctors, as far as I am concerned, have shown a high degree of responsibility in the use in this province of our hospital services. By deciding who shall be admitted and who shall be discharged.

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the medical profession wields a greater influence over the control of public funds than any other single group. The medical profession is really in charge of the "ship of health." I say this is the way it should be. After all, the medical profession, through an Act of the Legislature, has been charged with the responsibility for meeting the health needs of the people of the province, and it is only with the continued co-operation and concern of the medical profession that the stormy seas that lie ahead can be navigated. The government cannot do it alone. No government can do it alone. The trained professional people must be in charge. A safe course can only be charted with their active participation in every phase of health activity. The public accept this—the public look to the profession. The profession must strengthen this by working closely with their government and the public. Any program of health and welfare is only as good as the people want to make it. This includes all segments of the population. When people say that doctors have more responsibility than other people, they are really saying how dependent they are on the doctors. Everyone has a responsibility which can't be disregarded.

This most important field of endeavor, this field of endeavor that is closer to the vest of every man, woman and child in this province than any other, must of necessity be run by those who know what is best for the people. The medical profession is the first to admit they need public participation and concern. Surely there is room left for some voluntary effort and for some increasing responsibility, as we see the cost of this most essential service rising and rising. The government's role should be to give leadership, to co-ordinate the activities of all para-medical activities in this vast field, and to have policies which stimulate public concern. We hear more and more of the words "State Medicine," "State Controlled Programs." I believe that few people in Manitoba are anxious to see the state in complete control of medical care. I do feel, however, that the people of this province in the area of medical care do want to see these services made available to all.

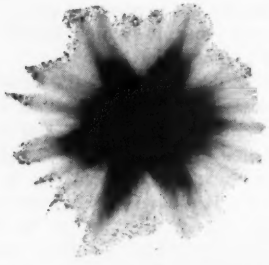
Society here has now reached a point of affluence where I think many of us here today believe that the essential needs of the people should be within reach and made readily available to all. This principle was enunciated by World Health Organization in that health is one of the basic rights of society. We have to accept the fact that the issue today is how best to bring in the most economical and most efficient way to make these health services available to all of the people. That is really the challenge facing the profession. This is where the profession and the government of the day must join in a partnership in meeting the needs of the people. Government and the profession have been charged with the health needs of the people. The medical profession has been given the right on University qualification to practice their art on the people without limitation, and the only policing that is carried on is done by the profession itself. This, we agree, is the only way in which health medical practice can be preserved.

The government is made up of the people, and it has become increasingly more involved in matters of health and welfare in that when the services of professional bodies are not readily available, the public turns to their representatives to find the answers. Now this is where government must turn to the profession to advise them as to how these needs are to be met. Without your professional knowledge, advice and ability, the medical needs of the people will never be met. By the same token, without government participation and support the profession cannot do it alone. In other words, as I have said earlier, it is a two-way street. You need the help of government to provide funds for clinics in outlying areas where local economy cannot support the professional man. I think you need government to assist you in providing medical services to those in need. By the same token, the profession should make their services available in terms of partnership with the government to meet the needs of the less fortunate. If the province's direct welfare responsibilities are looked after, the medical indigent is given a measure of relief and is able to obtain services when required, then, I believe, we should leave the rest of the population for voluntary participation. This, I think, is an ideal situation, and it would be wonderful to achieve this within our province. If the people's needs were being met, who is left to complain?

Now I come back to what I said earlier — should professional groups be unwilling and inflexible in their dealings with the government, and wish to maintain a standard fee schedule for all, and ask government to pay too much, in other words, price the public out of the market and the government out of the market for their services, then substandards of medical care will creep in. This is not a threat — it is a fact. You need government assistance in meeting the needs of these people—government needs the profession. The partnership in meeting need, I think, is the answer. What is the alternative?

The medical profession, more than any other profession, over the years has traditionally met need. No one quarrels with that statement. As World Health Organization announces health care is a basic right, as the Manitoba and Canadian Medical Associations in policy statements endorse comprehensive prepaid medical care, the pressures are on government to spell this out. This is the point.

This leads me to make a few remarks on our Manitoba program —Medicare. The philosophy behind this program I have indicated, the philosophy being to allow the government to join in partnership with the profession in meeting the needs of



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References: 1. Trussell, R. E.: New York Med. *13*:717 (Sept. 20) 1957. 2. Karnaky, K. J.: South. M. J. *51*:925 (July) 1958. 3. Decker, A.: New York J. Med. *57*:2237 (July 1) 1957. 4. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. *76*:666 (Sept.) 1958. 5. Weiner, H. H.: Clin. Med. *5*:25 (Jan.) 1958.

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the province's direct responsibilities. This is comprehensive care in partnership with the profession. In the province of Manitoba the profession has made an enormous contribution with government towards this program. As you know, we are forming a Commission to study the impact of comprehensive medical care programs on the teaching of medicine. Our terms of reference to this Commission are simple, "How do we maintain and enhance the teaching of medicine in the face of comprehensive care programs?" We feel this is the proper way to tackle the problem in that we could have spelled out the best comprehensive care program in the world, but if we did not have good doctors ten years from now, it would not be worth its salt. Medicare in Manitoba is limited to those who are in receipt of direct provincial assistance, and is an experiment in this field. Many problems are rearing their ugly heads, but they are only meant to be overcome. If they can be overcome during the next year or so under Medicare, it may pave the way for extension, for example, to cover medical indigency in a similar manner. I believe the professions and government must bear a great load for those in need, and as for medical indigents, I think government should bear a lesser load and the profession a lesser load, till finally you come to that line where people can readily participate in voluntary comprehensive coverage. With the eyes of the public on the profession, the profession we know in this province can and will respond. I think that government in partnership with the Medical Association of this province must sit down and establish those landmarks by which the profession's contribution should be measured in any extensions of Medicare. These landmarks must be set up clearly. The profession must take their share of the credit for their part in the program, and medical teaching must be preserved.

It is an interesting thing I have often heard doctors say to me, "Why do you want to come and purchase medicare when we are willing to do it for nothing as before?" This I do not agree with entirely, because in certain parts of this province this simply has not been so. Others say, "Why shouldn't the farmer give butter at half price to an old age pensioner, when you don't hesitate to ask the physician to cut his fees?" To these people I say this is where our responsibility as professional people comes in. The rights and privileges which we have been given by the law of the land surely places some responsibility upon us, and if we do not measure up to that responsibility, by this type of attitude, I can tell you we will get nowhere with the public. I believe firmly in the philosophy that if the needs of the people are met, who is left to complain?

Many of us know of smaller, possibly more rural practices where the words "state medicine" have never been mentioned. Where the dedicated medical practitioner is meeting the needs of his people, playing the real role of the physician, we hear nothing. To better meet the needs of his patients in rural Manitoba, I really feel a new era is coming upon us in that in order to ensure an increasing quality of medical care, it will become more and more necessary to centralize costly facilities at key points throughout the province. Many of the reasons for building very small hospitals at country points in the past were caused by transportation difficulties and other local factors which are now disappearing. For example, in order to extend efficiently laboratory and x-ray facilities to the whole of the population and to make them readily available to all physicians in the province will necessitate certain degrees of centralization of these services. The extension of diagnostic facilities is essential to prevent unnecessary admissions to hospital under our Manitoba Hospital Services Plan. Provision of adequate chronic facilities for the province, which is now being considered by the Willard Commission, the surveys which we have conducted re the problem of alternative care in this province, indicate very clearly from what I have seen to date that such facilities will have to be placed at key points.

As you all know, the continued advances made in medical science have and are resulting in individual doctors becoming more dependent upon other members of the profession specializing in various fields to diagnose and treat their patients. Medicine, in its modern concept, cannot be practiced successfully in many instances unless this fact is recognized. This dependence will continue to grow and will require a closer association between members of the profession in their work. We will, I am sure, in the future witness the development of larger hospitals, with a number of doctors admitting patients from their immediate areas, so that the advantages of consultation and co-operation between them will accrue to the patients. If changes such as this take place, the quality of medical care in rural areas will, I am sure, be improved, and this should result in medical graduates being more willing to establish practices at rural points. I would make a special plea for rural doctors, now that transportation and communications are greatly improved, to think seriously about working together in groups and through this association offering many advantages to the people in rural Manitoba.

As you know, to provide for the improvement of medical practice, my Departmental officials and representatives of your Association have been studying the possibility of having all tissues removed in a hospital, examined by a qualified pathologist. In respect to this matter, I would like to thank the Executive of the Manitoba Medical Association for the co-operation and assistance received in the studies made to date. In addition to this tissue service, we are most anxious to provide rural doctors with adequate laboratory and x-ray facili-

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ties in order to enable them to practice modern medicine. With this in mind my officials are actively examining this area.

I have already referred to the study being carried out by the Survey Board. This survey was instituted to ascertain the hospital situation in the province, and to make plans for an orderly development of any additional facilities which may be needed. We simply cannot allow hospital facilities to be established and extended without a properly developed program. The province is now paying 80% of the cost of hospital construction costs, and the total operating costs of hospitals, which are now approaching $6,000 per bed per year. These figures will give you some idea of the problems facing the survey board. Unnecessary hospitalization results in pressure for more beds, with all the resultant capital and operating costs having to be met through higher premiums and taxes.

In order to relieve the pressure on active treatment hospitals, we have been carrying out studies over the past year on how best to develop an overall program for those suffering from long term illnesses. This study indicates that nursing homes and other alternative facilities contain many elements of medical care which we are busily engaged in sorting out. In developing a program it is most essential to ensure that the various types of cases are placed in the type of facility best suited to meet their needs. In addition, by placing these different elements of medical care in separate facilities we may be able to bring those requiring medical and nursing care under the M.H.S.P. and make it easier for the welfare department to deal with the custodial type of case who cannot provide for himself. I might add that the classification of persons in the area between those requiring active medical and nursing care, and those merely requiring help with the daily problems of living, has been the most difficult problem with which we have been confronted. This problem is common to all provinces, so we are not alone. We feel now that we have made some progress in working out a solution.

Preventive medicine being the best medicine, we feel that the medical profession must think more and more in terms of the true assessment of the patient prior to alternative placement. As an expert in this field said to a group of doctors recently, "We mustn't just think of chronic patients going into lower cost facilities, there is no such thing as low cost facilities any more, nor anyone chronically sick. The patient is either sick, requiring medical and nursing care, or he can be more adequately cared for in his home, under home care programs, in a residence for the aged, where he requires some support with self-help activities, or in a form of rehabilitation." In other words, having spent all this time, effort and money in the province opening the front door of hospitals, we now have to find most efficient and humanitarian ways and means for opening the back door and following these people back into their communities. Increasing public health services by way of personnel, I think will accomplish more in many instances than spending additional amounts in bricks and mortar.

Having exhausted your good nature with a discourse of this length, I just want to leave these few words with our Association, Mr. President. I personally think that the Manitoba Medical Association and the Manitoba Medical Service are two of the finest organizations of their kind in Canada. The quality of medical care in this province is unexcelled. For every patient that leaves this province for medical care, four come into the province. Just don't get so efficient that we can't build you enough hospitals!

Thank you very much.

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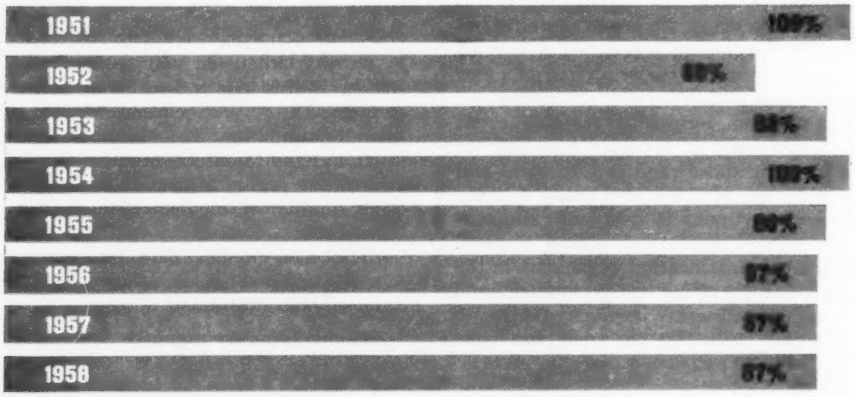

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References: (1) Rebhan, A. W., & Edwards, H. E.: *Canad. M. A. J.* 82:513, 1960. (2) Editorial Comments: *Canad. M. A. J.* 82:537, 1960. (3) Brownrigg, G. M.: *Canad. M. A. J.* 73:787, 1955. (4) Roy, T. E.; Collins, A. M.; Craig, G., & Duncan, I. B. R.: *Canad. M. A. J.* 77:844, 1957. (5) Royer, A., in Welch, H., & Marti-Ibañez, F: Antibiotics Annual 1957-1958, New York, Medical Encyclopedia, Inc., 1958, p. 783.

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Presidential Address

F. G. Allison
Retiring President

Mr. Chairman and Members of the Association:

The year's work is being covered in detail in the various committee reports but I wish to make a few brief comments.

To begin with, let me say how much I appreciate the honor and privilege of serving as your President during the past year. It was a very rewarding experience. The only untoward personal symptom was the development of a steak anorexia.

The most impressive experience of the year was the unanimity of all speakers at the General Council of the C.M.A. Annual Meeting in Banff on the evils of state medicine for patients, for the public purse, and for a regimented downtrodden profession. All speakers expressed support for and sympathy with the profession in Saskatchewan. Details of the C.M.A. principles on health insurance were hammered out phrase by phrase and word by word. The final form of this declaration was published in the public press and republished in the August-September number of the Manitoba Medical Review, page 561. I urge you to re-read this carefully, and keep it for reference.

The most important task of your Executive during the year was in co-operation with the Minister of Health and Public Welfare to produce the Medicare program for social assistance recipients, administered by the M.M.S. Ours is the first province in Canada to have such a plan administered by the doctor-sponsored prepaid medical plan.

Your Economics Committee is presently collecting facts and figures with a view to possible extension of full M.M.S. coverage to other low income groups with the help of subsidy.

During the year plans were completed for extending the study of all tissues removed at operation by committees of rural practitioners. Such tissue committees have improved the efficiency of surgery in large hospitals and it was felt that the time was ripe for extension of the system to rural areas.

Your Commitee on the Medical Aspects of Traffic Accidents under the Chairmanship of Dr. Norman Hill, is actively studying methods of minimizing the toll of the roads as will be seen in the report. On the recommendation of Mr. Bailey of the Motor Vehicles Branch of the Department of Public Utilities and of the Traffic Accidents Committee, your Executive has appointed a Consulting Board to advise on fitness to drive of persons referred by Mr. Bailey or by their own doctors. A study of rural ambulance service has also been initiated.

In conclusion, I would like to thank the members of the Executive Committee and of all other committees for their untiring work. My best wishes go to the incoming Executive. Our special thanks go to Dr. Max Macfarland and all members of his staff, particularly Mr. Sprague, Miss Graham and Miss Bogden.

Delivered at the Annual Meeting of the Manitoba Medical Association, 1960.

Invitation to Manitoba Medico-Legal Society

Every member of the medical profession is invited to take an active part in this year's program of the Manitoba Medico-Legal Society. Its first meeting was held at 8 o'clock, Tuesday the 25th day of October, 1960, at Theatre "A" Manitoba Medical College.

The basic pattern to be followed this year at most of the meetings shall be the delivery of two twenty-minute long, prepared papers by a lawyer and a doctor, followed by an open discussion in which everybody including the audience shall join in. The executive have made a real effort to select meaningful topics which will provide an interesting challenge to both professions. The first topic dealt with on October 25th, 1960, was "Abortion and Sterilization." The prepared papers were delivered by Dr. Elinor F. E. Black and Mr. J. F. Reeh Taylor. The second meeting will be held on Tuesday, November 22nd, at 8 p.m., to discuss the topic, "Human Rights and Hospitals" and the prepared papers will be delivered by Dr. Paul L'Heureux and Mr. Arthur E. Johnston, Q.C. Other topics to be dealt with at future meetings are "Who is Fit to Drive" and "Your Income Tax Problems." It is proposed to reserve the fifth meeting for some outstanding speaker who may be available for such purpose in the weeks that lie ahead. Any suggestions as to whom such a speaker should be would be appreciated. The executive also decided that the meetings would open promptly at 8 o'clock and close precisely at 10 o'clock. For those who are to indulge in post-meeting camaraderie, coffee and sandwiches are provided.

Applications for membership this year should be sent to Mr. G. O. Jewers, 4th floor, 356 Main Street, Winnipeg 1, Manitoba — the new secretary of the Society. The fee for doctors who have practised more than five years is $5.00. For those who have practised less than five years, the fee will be $2.00, and for medical students, the fee is $1.00. Every member of the medical profession and every medical student is invited to apply now and to remit his fee with the application.

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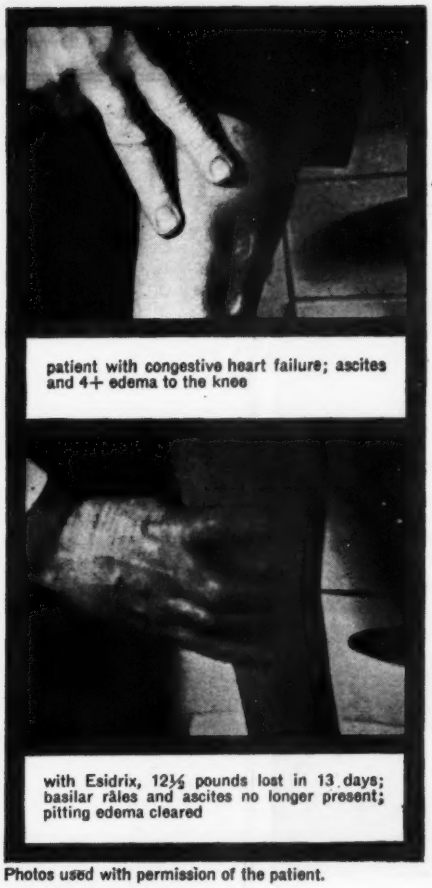
OUR PRESIDENT 1960 - 1961

Dr. Harvey Lawrence McNicol was born in Wadena, Saskatchewan, in 1911, where he attended Public School and High School. Following this he came to this province to attend the University of Manitoba, graduating in Medicine in 1935. He spent three and a half years interning at the Winnipeg General Hospital, two years as a resident in surgery.

In 1937 Dr. McNicol commenced practice in Flin Flon but two years later he joined the Army and served overseas with Number 5 General Hospital for three years and one year at Deer Lodge Hospital. In November, 1945, he returned to Flin Flon.

Dr. McNicol received his certification in General Surgery with the Royal College of Physicians and Surgeons of Canada in 1946 and was made a Fellow of the American College of Surgeons in 1955.

From 1955 to 1958 Dr. McNicol ably served the North of 53 District Medical Society as a representative to the Executive Committee, and became Second Vice-President in 1958, being installed as President at the Annual Dinner on September 29th, 1960.



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Editorial

S. Vaisrub, M.D., M.R.C.P. (Lond.), F.R.C.P. (C.), F.A.C.P., Editor

Diabetes

Medicine is cleft into many specialties. Organs, systems, age, even diagnostic and therapeutic techniques have served conveniently as planes of cleavage. Occasionally, by dint of special circumstance an individual disease entity would find itself split off the body of general Medicine to become a specialty. This fate befell tuberculosis because of segregation of its victims in specialized institutions. This was also the case with syphilis in the pre-penicillin era due to the social connotations of the disease, its clinical versatility and its resistance to therapy. This is now happening to Diabetes.

That Specialism is now catching up with Diabetes is attested by the numerous diabetic associations, diabetic publications, and by the growing number of physicians who devote their time predominantly or exclusively to the care of diabetic patients. But just why this is happening is not at all clear. It certainly is not because of the high incidence of the disease. Coronary disease, hypertension and peptic ulcer are more common than Diabetes, yet to date they have laid no claim to specialty status. Nor can the reason lie in the high mortality or morbidity of Diabetes, for here again there are other more worthy contenders. Perhaps, it is the "ritualistic" aspect of this disease which sets it apart from other afflictions. The pre-occupation with diet, the rite of insulin administration, the ceremonial of urinalysis involve the patient and the doctor in an intimate and often time-consuming relationship. The physician who looks after many diabetics may find little time or energy left for any one else.

Yet, Diabetes does not quite fit in the narrow confines of a specialty. The diversity of its manifestations, concomitants and complications militates against its being tethered into a restricted field. Resting on a broad base of biochemical science, incorporating into its structure a variety of pathophysiological disturbances which affect a number of organs and organ systems, it has an appeal to which no doctor can remain indifferent. Atherosclerosis, gangrene, neuropathy, myelopathy, nephropathy, oculopathy, ketoacidosis, infections — all and each have something to offer to every physician whether he be a specialist or generalist.

It is the catholicity of the appeal of Diabetes which the Review hopes to exploit in offering its readers the Symposium Issue. As the wide panorama of the disease unfolds before his observing eye, almost every reader will be sure to find sights of special interest to absorb his attention. Should anyone, however, fail to find his favorite sector given sufficient prominence in this magnificent view, let him bear in mind that comprehensiveness is the desideratum of textbooks, not of short symposia. Omissions are to be expected, and — it is hoped — condoned.

There is one sin of omission, however, that can never be forgiven. No work on Diabetes, whatever its size, may be allowed to omit a reference to the discoverer of Insulin. Not to mention the name of Sir Frederick G. Banting, would be tantamount to gross irreverence. It would also be most ungrateful, for not only do countless victims of Diabetes owe him a debt of life and health, and all doctors the debt of enhanced self confidence and peace of mind that comes from added power of healing, but also the basic scientists, particularly the biochemists are indebted to him for the vast amount of new knowledge and understanding of the processes of metabolism and growth that his discovery brought in its wake. To quote Charles H. Best: "The search for the complete explanation of the action of insulin has stimulated so many aspects of physiology and biochemistry that there may be a sense of loss when the goal is fully attained."

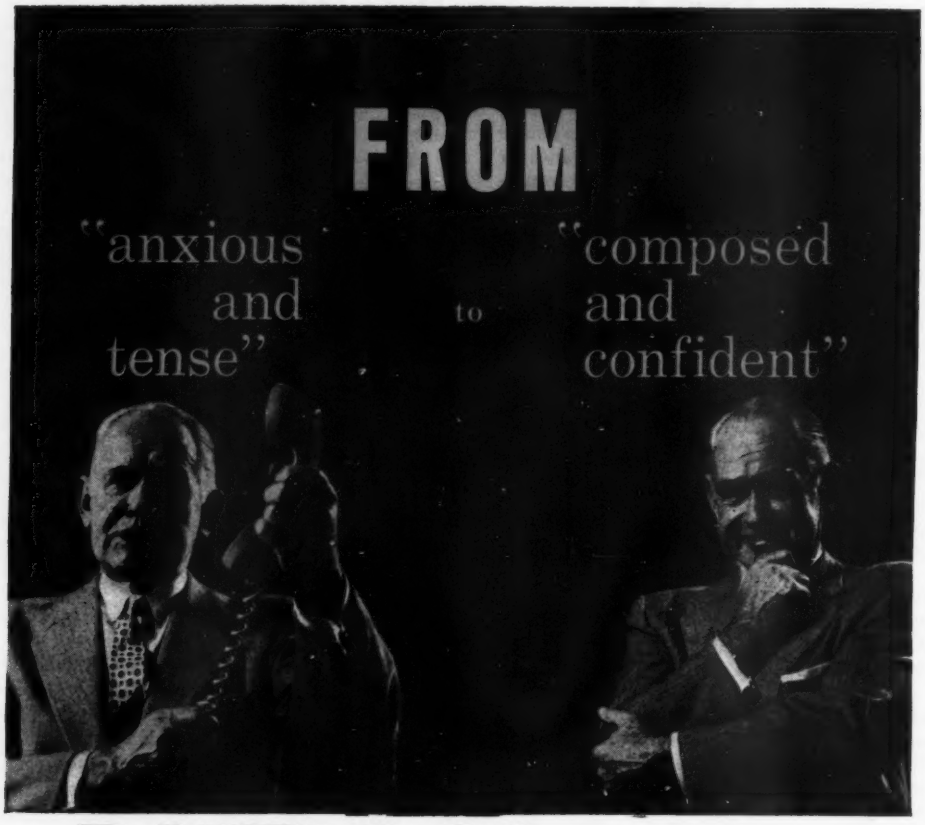
Indeed no other discovery illustrates more clearly this fascinating relationship between the Clinical and the Basic, wherein a great scientific discovery, prompted by an urgent clinical need, not only fills this need, but in turn stimulates further researches into the Fundamental — a relationship replete with promise of unlimited progress for both Science and Clinical Medicine.

Ed.

Book Review

Diabetes: With a chapter on hypoglycemia. By 54 authors. Edited by Robert H. Williams, M.D., Executive Officer and Professor of Medicine, University of Washington School of Medicine and Physician-in-chief, University Hospital, Seattle 8, cloth, 810 pp., with 192 illustrations, 23 in full color and several tables. New York: Paul B. Hoeber, Incorporated, 1960. $20.00.

Gone are the days when a comprehensive textbook of Medicine could be written by one author, single handed and unaided. Almost all standard medical texts nowadays are products of multiple authorship. The only remaining outlet for an individualistic medical writer, aspiring to a book of his own creation is a narrow subspecialty. Alas! This outlet too is being rapidly choked off. Subspecialties are expanding at a rate which precludes an encircling embrace by a single individual, competent as he may be. To appreciate this fact one



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1. Grossman, A. J.: Batterman, R. C., and Leifer, P.: Fed. Proc. *17*:373 (March) 1958.

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has only to glance at the book under review which boasts of 54 authors, each an authority in his field.

This book also boasts of 48 chapters, 810 pages and 192 illustrations. Formidable as these figures may appear, they need not overawe the reader. The book is absorbingly readable. Written as stated by its editor, for "internists, basic medical scientists, and students," it refutes the old maxim that he who tries to please everyone will end up by pleasing no one. Indeed, it succeeds in pleasing everyone, whether he be a basic scientist, a clinician or a student. The basic scientist will find an abundance of scientific information in the first 26 chapters dealing with diabetes in the wider context of general metabolism, enzymo-endocrinology, histopathology and histochemistry. The clinician will find a wealth of useful data in the remaining 415 pages devoted to diagnosis, prognosis, concomitants, complications and therapy. The student will enjoy both the basic and the applied, but best of all the concise summaries and conclusions that follow most of the chapters. All will enjoy the fresh approaches, the occasional conflicts of viewpoints and even the unavoidable overlap and repetition, which are the earmarks of every worthwhile book of multiple authorship.

The caliber of the authors is of the highest. Each is famed for original research into the facet of Diabetes that he is presenting, thus giving it "straight from the horse's mouth" touch that enhances its authoritativeness.

The book is highly recommended.

Ed.

Obituaries

Dr. Walter Felix Tisdale

Dr. Walter Felix Tisdale, 73, died on September 29th. Born in Greenway, Manitoba, of U.E. Loyalist stock, he attended Baldur High School and graduated from Manitoba Medical College in 1917 with honours and the general proficiency medal. He served in France with the R.A.M.C. then was seconded to a British Field Ambulance attached to the 30th American Army Division. At the end of the war he did post-graduate work, practised for two years at Russell, then worked for the Red Cross in the Northern Lake district. In 1925 he began practice in Winnipeg in the Riverview district associating himself with Misericordia, Grace and Victoria hospitals of which latter he was chief of staff. He became secretary, then president of the Winnipeg Medical Society in 1945 and set in motion the Winnipeg Medical Society Benevolent Fund.

The title of his presidential address before this Society was "Nature, That Dear Old Nurse." In words that were the true stuff of poetry he spoke of the beauty of nature which has been an uplift and inspiration to man. He was interested in the conservation of wild life and this interest found practical expression when he became director and president of Ducks Unlimited (Canada), Manitoba Game and Fish Association and president of Manitoba Museum Association. Of special interest to him were the great whooping cranes, now almost extinct and more than once he visited the sanctuary established for them in Texas. Though not a hunter, he was the 1931 Manitoba champion in trapshooting.

In 1953-54 he was President of the Manitoba Medical Association and later was chairman of the board of Manitoba Medical Service sponsored by that association.

He and his charming wife delighted to extend hospitality. She survives him as do two brothers, Dr. John E. and Charles, and two sisters. He was a man of many parts, of warm generous disposition and alive to beauty in all its forms.

☆

Dr. Earl Stewart Bolton

Dr. Earl Stewart Bolton, 76, of Brandon died in Winnipeg, September 19th. He graduated in 1909 from Manitoba Medical College and practised in Brandon from 1914 to 1931 when he became Medical Health Officer for Brandon. He held this post until 1951 when illness compelled him to resign. For many years he was soloist in the First Church United at Brandon and took part in the annual Kiwanis Minstrel show. He is survived by his wife, a son, a daughter, and eight grandchildren.

☆

Dr. William John MacTavish

Dr. William John MacTavish, 85, of North Surrey, B.C., died there on September 18th. Born in Wellsley, Ontario, he came to Manitoba in 1896 and graduated from Manitoba Medical College in 1905. He practised in Altona then in Winnipeg from 1907 till 1939 when he went to New Zealand. In 1948 he returned to Winnipeg until he retired in 1954. He is survived by two sons, two daughters, ten grandchildren, a sister and three brothers, two of whom are Dr. James A. and Dr. G. Boyd of Winnipeg.

for the new diabetic*
a safe and smoother route
Mobenol and diet provide a safe, smooth, and painless journey through the years for the tolbutamide-responsive diabetic. The negligible risk of hypoglycemic reactions, greater freedom, and generally better control permit the Mobenol-managed diabetic to lead an almost normal life.
Do not these profound objective and subjective benefits suggest that every mild, non-ketotic diabetic deserves an adequate trial on Mobenol therapy? Less than one month's evaluation will decide most cases.
*of the mild, non-ketotic type.
ORAL DIABETES THERAPY
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Association Page

Manitoba Medical Association Election Results

As a result of the recent election, the following Officers and Members-at-Large are now on the Executive Committee:

President:
Dr. H. L. McNicol, Flin Flon.

First Vice-President:
Dr. K. R. Trueman, Winnipeg.

Second Vice-President:
Dr. K. I. Johnson, Pine Falls.

Honorary Secretary:
Dr. F. W. DuVal, Winnipeg.

Honorary Treasurer:
Dr. W. S. Neal, Winnipeg.

Winnipeg Member-at-Large:
Dr. R. O. Flett, Winnipeg.

Rural Member-at-Large:
Dr. G. T. McNeill, Carberry.

The nominee for Senior Membership in the Canadian Medical Association for 1961 is Dr. D. F. McIntyre, Winnipeg.

Nominees to the Board of Trustees, Manitoba Health Service for a three-year term from March, 1961, are:

Dr. G. L. Adamson
Dr. E. G. Brownell
Dr. N. I. Corne
Dr. G. P. Fahrni
Dr. A. G. Henderson
Dr. R. T. Ross.

Quorum

It seems to be the general consensus of opinion that the recent Annual Meeting was successful. From a registration point of view — 564 recorded as attending — one would say, very good!

But — what happened to our members when the business session started? This is supposedly the time to see democracy in action. All members may have their say and speak their mind.

Why then, was it necessary to send a press gang through the darkened corridors to seek sufficient members to form a quorum?

How many required for a quorum? 100? No sir, just 30 ordinary members!

How long can we afford to "let George do it"? Perhaps our neighbor to the west has the answer. Have you?

Tissue Committees

More than a year ago the Hospital Relations Committee reported to the Executive that it was its intention to recommend to the 1959 Annual Meeting that, "a committee be constituted to investigate the feasibility of a Central Tissue Registry." The report was so presented to the Annual Meeting and received approval.

Although this appeared to be something new, it was pointed out that centralized Government-sponsored tissue committees have existed in other provinces for many years and such committees would be formed in Manitoba if the profession would not accept the responsibility. It was obvious that these committees should be constituted as quickly as possible in order that discipline, if necessary, should remain in the hands of the profession.

During the course of the past year, many meetings and discussions were held with those groups concerned and finally the idea began to emerge in its present form following meetings with the M.H.S.P. Division of Standards. In order that hospitals may play their part, a regulation under the Hospitals Act was necessary, to provide for the handling and investigation of tissues. This was drafted by the M.H.S.P. and approved by the Association. The regulation appeared in the Manitoba Gazette, September 24th, 1960, and is reprinted here for your information.

"Schedule "A" — Manitoba Regulation 51/60— Being A Regulation under the Hospitals Act to provide for the handling and investigation of tissues in hospitals."

1. In this regulation

(a) "Area Tissue Committee' means, with respect to any hospital, the committee designated in writing to that hospital as its tissue committee by the Manitoba Medical Association.

(b) "hospital" has the same meaning as in the Hospitals Act and includes, with respect to hospitals established under the Health Services Act, The Governing Board of a Hospital District and The Governing Board of a Medical Nursing Unit District;

(c) "Pathologist" means a person registered in that specialty with the College of Physicians and Surgeons of Manitoba;

(d) "Tissue Committee" includes a medical audit committee.

2. Every hospital shall

(i) take possession of and suitably preserve all tissues removed from any person during an operation in the hospital;

(ii) obtain a statement from the surgeon removing the tissue setting forth the reason for its removal, together with pertinent clinical data;

and the statement so obtained and suitably identified shall be kept with the tissue at all times

Robitussin helps remove the cause of cough[1]

Glyceryl guaiacolate (Robitussin) exerts "the most intense and prolonged"[2] expectorant action "of practically all drugs presently used clinically as expectorants."[2] It increases the secretion of Respiratory Tract Fluid almost 200 per cent.[2]

Increased R.T.F. helps liquefy sputum,[2-4] making it less viscid and easier to raise[3] and enabling the upward-beating tracheal and bronchial cilia to become more efficient.[3,5]

And increased R.T.F. provides a demulcent effect that helps soothe dry, irritated membranes lining the respiratory passages.[1-3,6]

Through these "significantly superior"[2] expectorant effects, Robitussin increases the probability that a cough will achieve its natural purpose—that is, to remove irritants such as exudates or mucus from the respiratory tract.[1,4,5]

Robitussin®

glyceryl guaiacolate, 100 mg., in each 5 cc. teaspoonful

Robitussin® A-C

glyceryl guaiacolate, 100 mg.; prophenpyridamine maleate, 7.5 mg.; and codeine phosphate, 10 mg.; in each 5 cc. teaspoonful

Oral prescription narcotic product

references: 1. Blanchard, K., and Ford, R. A., Journal-Lancet, 74:433, 1954. 2. Cass, L. J., and Frederik, W. S., Am. Pract. Dig. Treat., 2:844, 1951. 3. Hayes, E. W., and Jacobs, L. S., Dis. Chest, 30:441, 1956. 4. Blanchard, K., and Ford, R. A., Clin. Med., 3:961, 1956. 5. Blanchard, K., and Ford, R. A., Rocky Mt. M. J., Vol. 52, No. 3, 1955. 6. Boyd, E. M., et al., Can. M. Assoc. J., 54:216, 1946.

A. H. Robins Company of Canada, Ltd., Montreal, Quebec

3. Where a hospital takes possession of any tissue, it shall cause the same to be investigated by a pathologist, and, for that purpose, shall deliver the tissue to him forthwith and in good condition.

4. (1) Subject to subsection (2), the investigation of all tissues shall include the identification thereof and such examination and disposal as the pathologist may consider advisable.

(2) Except where otherwise directed by the surgeon who removed the tissue, the investigation may be completed without any examination, except identification in the following cases:

(a) Amputation stumps — secondary
(b) Placenta
(c) Bone fragments and ligaments
(d) Bony ossicles (ears)
(e) Cartilage, external ear (plastic)
(f) Fingers
(g) Foreign bodies (including bone plates, nails and screws)
(h) Hernial sac
(i) Hydrocele sac
(j) Intervertebral discs
(k) Nasal septa when removed for obstruction only
(l) Meningocele sac
(m) Optic lens
(n) Prepuces under 25 years of age
(o) Ribs removed incidental to chest surgery
(p) Scar tissue
(q) Semilunar cartilages
(r) Teeth
(s) Tendon segments removed incidental to orthopaedic procedures
(t) Toes
(u) Toe and finger nails
(v) Tonsils and adenoids under 25 years of age
(w) Vaginal wall fragments (plastic repair)
(x) Varicocele
(y) Vein strippings

5. Where a hospital has caused a tissue investigation to be made it shall procure copies of the pathologist's report on the investigation and file one copy:

(a) with its Tissue Committee or with its Area Tissue Committee
(b) with the surgeon who removed the tissue
(c) in the hospital's laboratory
(d) in the patient's medical record, and
(e) where the pathologist considers it advisable, with the Cancer Foundation.

6. Every hospital having a Tissue Committee shall cause all pathologist reports on tissues removed from patients in the hospital to be reviewed regularly by that committee."

On July 7th, 1960, a letter was sent to the Commissioner, M.H.S.P. indicating that the Manitoba Medical Association would undertake to establish area committees to act as tissue committees for those hospitals the Association considered to have an insufficient number of attending doctors to form such a committee. An insufficient number was considered less than three doctors. The terms of reference of such area committees was set out in the letter as follows:

(a) To examine all tissue reports
(b) To study all charts in which laparotomy or thoracotomy has been performed and where no tissues were removed.
(c) To keep a tissue audit of each doctor who attends the hospitals which are in the category described above.
(d) To send a summary of findings to the Manitoba Medical Association after each meeting.

The subject of tissue committees was discussed at various Regional District Society meetings and it was an accepted fact that the District Societies play a major part in the actual formation and operation of the committees. The number of area committees required or desirable was considered but no definite number was established as it was felt desirable that this phase and also the mechanics of operation be subject matter for a meeting of all District Medical Society representatives.

This meeting was held on September 28th, 1960, at which time there was approval in principle of forming area tissue committees, that there be free choice of pathologist and that District Societies be responsible for the formation of such committees.

Studying the situation geographically the meeting agreed that it was practical to establish five area tissue committees defined as follows:

District No. 1—Between the Lakes converging to Winnipeg and then East of the Red River and South to Highway 23, excluding Metropolitan Winnipeg. Centering on Selkirk.

District No. 2—Central District Medical Society plus Southern District Medical Society centering on Portage la Prairie.

District No. 3—To include Brandon and District Medical Society and Northwestern Medical Society, centering on Brandon.

District No. 4—Northern Medical Society centering on Dauphin.

District No. 5—North of 53 Medical Society centering on The Pas.

It was suggested that hospitals that are now accredited or those hospitals that now have their own tissue committees not be included in the programme as it was felt that if tissue committees are in a centralized area the control and educational value will be lost for the rural areas. It was pointed out however, that it may be practical to have the tissue headquarters in an area where there is a fairly large hospital with office staff and equipment in order that the staff could do preliminary documentary work for the committee.

It was the decision of the meeting that representatives take the matter back to their Districts for further discussion and planning.

The target date to have committees in operation is early 1961. R.P.H.S.

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BRAND OF PROPANTHELINE BROMIDE WITH PHENOBARBITAL

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calm
relief
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RATIONAL NEW ANTISPASMODIC FORMULATION:

propantheline bromide (7.5 mg.) / and phenobarbital (15 mg.)
the standard for control of gastrointestinal spasm / the standard for augmenting antispasmodic action
compression-coated tablets

Probital provides rational, convenient therapy in smooth-muscle spasm: spasm of the pylorus, small and large intestines and the sphincter of Oddi, as well as gastritis, biliary dyskinesia and diverticulitis.

Questions and Answers Page

In order to keep the medical profession informed as fully as possible in all matters relating to Association business, medical economics and prepaid medical care, this page welcomes questions pertaining to these fields.

This month's question was selected from a doctor who wished to know about M.M.S. His question can be broken down in 3 parts:

(a) What types of contracts does M.M.S. offer to the general public?
(b) What are the current premium charges?
(c) Are there any restrictions as far as age or coverage is concerned for new applicants?

Answer:

It should be mentioned firstly that M.M.S. is recognized as one of the "top" plans on the North American continent, not because of geographic location but primarily because of the broad coverage offered and very limited restrictions.

The M.M.S. operates on a group and non-group basis with group contracts far outnumbering the non-group enrolment. For the uninitiated, a group contract is one arranged through a place of business and may or may not enjoy "employer contribution." Recent M.M.S. information indicates that there are close to 1,700 groups and in approximately half of these groups the employer makes some contribution toward the premium. A group may be formed with as few as 5 employees.

Non-group, as the word implies, is the enrolment of those individuals who do not have group affiliation. They make application and remit their premiums directly to M.M.S.

Our questioner asked about the various contracts available. These can best be described in terms of "Benefits" that the following plans offer.

Plan H — This Plan includes provision for services of a legally qualified medical practitioner while a subscriber or dependent is a registered and admitted bed patient (IN-PATIENT) IN A PUBLIC GENERAL HOSPITAL. The range of services provided includes:

1. Medical services — no limit on days.
2. Surgical services, including services of assistant surgeon when necessary.
3. Services for treatment of fractures and dislocations, burns and lacerations.
4. Maternity services.
5. Services of anaesthetist, when surgery or maternity is covered.
6. Services of consultant, when necessary.

Plan HC — This Plan includes in addition to the services of Plan H, the full range of services included under Plan H when provided OUT OF HOSPITAL, i.e., at the patient's home or in the physician's office.

This plan does not include the additional services described under Plan HCX.

Plan HCX — This Plan includes in addition to the services of Plan HC, the following services when rendered in a physician's office:

1. X-ray services.
2. Medical treatment including immunizations, injections, allergy care.
3. Medical examinations and tests — including basal metabolism tests, heart tracings, brain tracings, ear tests, eye tests, etc.
4. Laboratory services — including blood tests, gastric analysis, etc.

As you can see, Plan H is the basic contract providing services when the subscriber is a bed patient in a public general hospital. Plans HC and HCX provide progressively broader benefits which reflects in the premium rates. They are, of course, obtainable for individual or family coverage.

Without delving too deeply into experience rating which is a method of having the premium bear some relationship to the group's claims experience, the monthly rate for an average size group is as follows:

	Plan H	Plan HC	Plan HCX
Individual	1.00	2.60	3.30
Family	3.00	6.60	8.25

Due to the extra expense of individual enrolment and premium collection in non-group business and possibly claims experience, non-group rates are proportionately higher than group. Be careful when comparing, as the following non-group rates are on a **quarterly** basis:

	Plan H	Plan HC	Plan HCX
Individual	3.75	8.25	10.50
Family	10.50	24.00	30.00

Our questioner has asked about restrictions. There are sensible limitations applied to new applicants, both group and non-group. These refer to maternity coverage — both husband and wife must be members on the same contract for 270 days. Pre-existing conditions are not covered during the first 12 months of membership and services for the following are not covered during the same period of time:

Adenoids, Tonsils, Nasal and Paranasal conditions, Hernia, Veins, Refractions or eye-testing, Sterility investigation or medical or surgical procedures on the genital system.

There are other restrictions that should be mentioned in the form of "underwriting" rules concerning non-group applicants. They must not be employed where there are 5 or more employees and may have Plan H if age 65 or over, Plan HC if under age 65 and Plan HCX if under age 55.

It can be seen from this that an individual is unable to purchase M M.S. coverage when employed where there are 5 or more people and the staff does not wish to enrol in M.M.S. It is felt that there should be a better answer to this than denial of coverage. It is a problem worthy of our serious consideration.

WHENEVER COLD SYMPTOMS STRIKE

1 2 3 RELIEF

"123" TABLETS ("Pyrithen" w. Codeine 1/8 gr.)

FORMULATED FOR FAST RELIEF

1 Preferred analgesic-antipyretic-antitussive

Acetylsalicylic acid	200 mg.
Phenacetin	150 mg.
Caffeine	30 mg.
Codeine phosphate	1/8 gr.

2 Superior antihistaminic

Carbinoxamine maleate	3 mg.

3 Essential factor for tissue repair

Vitamin C	100 mg.

In bottles of 12 and 40 tablets.

WHEN DISCOMFORT IS MORE SEVERE

Ⓡ **"124" TABLETS** ("Pyrithen" w. Codeine 1/4 gr.)

Same basic formula but with codeine 1/4 gr.

ADULT DOSAGE—One tablet three or four times daily.

CAUTION: Drowsiness is minimal with carbinoxamine maleate. Patients subject to this reaction, however, should avoid driving a car, operating intricate machinery or doing work that requires fine precision.

Ⓡ *Telephone narcotic prescription permitted.*

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Social News

Reported by K. Borthwick-Leslie, M.D.

Our loss is California's gain! Grace Hospital and Staff bade a fond farewell to Dr. S. M. (Slug) Lugensky a few weeks ago, when he complete with family took off for warmer, greener fields. The last reports are glowing. Pleasant trip — temporary address, 604 Island View Drive, Seal Beach, California. At present Slug is associated with the Westwinster Hospital, new hospital, new district. More anon, when I hear from him.

☆

Dr. Gerd Fischer has been attending a Neurosurgical conference in Naples, prior to joining Mrs. Fischer and family, in Frankfurt, Germany, where they have been holidaying since May. Dr. Fischer, with family, expects to return about the middle of November.

☆

Congratulations to Dr. R. L. Rabson on his appointment as Chairman C.M.A. Committee on Prepaid Medical Care, also as a member of the C.M.A. Advisory Committee to the Federal Government.

☆

Dr. Christina Curran, having attended the American Academy of Paediatrics in Chicago last week, reports an excellent meeting. Drs. Briggs, Coodin and Baisley also attended. Chris enjoyed meeting Dr. Anna Wilson Sharpe, now of Ottawa, who says "Hello" to Winnipeg.

☆

Charles Neville Crowson, M.D., Ph.D., certified Pathologist, announces the opening of a branch office of Central Medical Laboratories Ltd., in Ste. 21, Medical Arts Building. Practice restricted to Clinical Pathology.

November 9th. The 1960-61 Executive of the Manitoba Branch of the Federation of Medical Women of Canada will honor the undergraduates of Medical Women. Buffet supper, etc., at the home of Dr. Donna (Randall) Semelka, 546 Cambridge Street.

☆

Speaking of the Federation, I find in the report of the meeting in Banff, June 1960, that one "Dr. K. Borthwick-Leslie of Winnipeg was elected to Senior Life Membership of the Federation." Good heavens, I don't feel that senior! Slate of officers for the year familiar to us are — Past President, Dr. Jessie McGeachy, Saskatoon; Treasurer, Dr. Donna Semelka, Winnipeg; International Corresponding Secretary, Dr. Marie Storrie, Winnipeg.

☆

There were so many babies reported last time, the stork must have taken a holiday.

☆

Dr. and Mrs. Alvin Elliott announce the arrival of Lawrence John, October 6, 1960, in Brandon, Man.

☆

Dr. and Mrs. J. Macdonnell, October 20, 1960, Victoria, B.C., a daughter, Ann Kimberley.

☆

Dr. and Mrs. Erwin Penner are pleased to announce the birth of their third son, Timothy Otto Erwin, October, 1960.

Indicated in Amenorrhea and at the Menopause

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TABLETS

NATURAL OESTROGENIC HORMONES

PLAIN:

For Oral Estrogenic Therapy
Each tablet contains 0.65 mgm. (6,000 I.U.)
of Coniugated Estrogenic Substances

DOSAGE: 1 to 3 tablets daily.

WITH PHENOBARBITAL:

For Oral Estrogenic Therapy with Sedation
Each tablet contains 0.65 mgm. (6,000 I.U.)
of Conjugated Estrogenic Substances and
Phenobarbital 30 mgm. (½ gr.)

DOSAGE: 1 to 2 tablets daily

Bottles of 25 and 100 tablets

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MONTREAL **CANADA**

HOSPITAL MEETINGS

Hospital	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Children's	12:00 Surgical Rounds	10:00 Staff Rounds "B" Service 12:00 Postgraduate Seminars	9:30 Staff Rounds "C" Service 11:00 Clinical Path. Conference	11:00 Grand Ward Rounds	10:00 Staff Rounds "A" Service	9:00 Newborn Conference
Deer Lodge	Clinical Luncheon (1st Monday)			11:00 Ward Rounds		
Grace	12:00-2:00 p.m. Weekly Seminar	Clinical Luncheon (3rd Tuesday)		12:00-2:00 p.m. Weekly Seminar		
Misericordia		2. Clinical Luncheon				
Municipal			7:30 p.m. Review of Deaths (2nd Wednesday)			8:30 Clinical Staff Conf. and Ward Rounds
St. Boniface	11:00 Paediatric Rounds	11:00 Surgical Rounds	11:00 Grand Rounds 11:00 Cardio-Pulmonary Conf. (2nd Wednesday)	8:00 Orthopedic Rounds 11:00 Tumor Clinic 11:00 Obstetrical Rounds 12.00 Clinical Luncheon (2nd & 4th Thurs.	11:00 Medical Rounds 11:00 Cardio-Pulmonary Conf. (4th Friday)	
St. Boniface Sanatorium		12:30 Clinical Luncheon (2nd Tuesday)				
Victoria		Tissue Committee (1st Tuesday)			3. Clinical Luncheon 4. Active Med. Staff	
Winnipeg General		11-12:00 Medical Ward Rounds	9-10:00 Tumor Clinic 10-11:00 Surgical	12:15 Clin. Lunch. (1st & 3rd Thurs.)		
Brandon General			Medical Staff Lunch (Wed. prior to 2nd Tues. each month)			10:00-noon Clinical Drs. from S.W. Manitoba invited (Nov. to May)

(+)=(0) DESBUTAL GRADUMET

A Release Pattern So Carefully Synchronized

each half releases its own drug in "harmony" to the other (no more "peaks and dips")

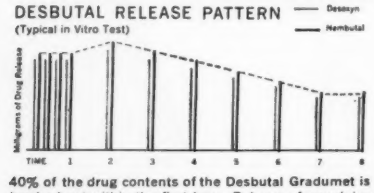
With the precision of a finely-made watch, the long-acting Gradumet is timed to expel its drug contents throughout the day.

Desbutal® Gradumet® consists of two halves (Desoxyn® and Nembutal®, each in its own matrix) which are fused to form an inseparable, single tablet. Each half is specially-engineered with its own release rate to insure that the combined effect is harmonious in onset and decline. See chart.

Note the absence of "spread" between the two drugs over the 8-hour period. This insures that an optimal ratio of the two ingredients will be made available to the patient at all intervals during the day.

Indicated for anoretic effect in obesity; also for counteracting depression associated with anxiety, and tension in psychosomatic disorders, neuroses, mild psychoses and other conditions. Usual all-day dosage is one Desbutal Gradumet. In two strengths, Desbutal 10 Gradumet (10 mg. of Desoxyn and 60 mg. of Nembutal) and Desbutal 15 Gradumet (15 mg. of Desoxyn and 90 mg. of Nembutal).

DESBUTAL RELEASE PATTERN
(Typical in Vitro Test)



40% of the drug contents of the Desbutal Gradumet is leached out within the first hour. Release of remaining drugs continues during the following seven hours. Dotted line shows the smooth, steady release pattern.

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DEPARTMENT OF HEALTH & PUBLIC WELFARE

COMMUNICABLE DISEASE PICTURE

LIST OF DEATHS FROM COMMUNICABLE DISEASES
September, 1960

URBAN: Cancer, 93; Diarrhoea & Enteritis, 9; Diphtheria, 1; Influenza, 1; Measles, 1; Meningitis (meningococcal), 1; Pneumonia Lobar (490), 2; Pneumonia (other forms), 20; Poliomyelitis, 1; Septicaemia & Pyaemia, 1; Tuberculosis, 2; Whooping Cought, 1; Dysentery, unspec., 1. Other deaths under 1 year, 34. Other deaths over 1 year, 343. Stillbirths, 25. Total, 536.

RURAL: Cancer, 20; Diarrhoea & Enteritis, 4; Influenza, 1; Pneumonias (other forms), 4; Tuberculosis, 2. Other deaths under 1 year, 14. Other deaths over 1 year, 128. Stillbirths, 5. Total, 178.

INDIANS: Diarrhoea & Enteritis, 2; Measles, 1; Pneumonias (other forms), 1. Other deaths under 1 year, 0. Other deaths over 1 year, 2. Stillbirths, 1. Total, 7.

Unorganized Miscellaneous

A case of anterior poliomyelitis was reported from South Indian Lake in a seventeen year old male. This patient had received at least one dose of polio vaccine.

General

The two cases of poliomyelitis reported during the month brings the total to date for 1960 up to nine. Infectious hepatitis continues to be prevalent with fifty-nine cases being reported. Otherwise communicable diseases during the month has been comparatively small.

North of 53 District

One case of infectious hepatitis, a case of meningitis due to other unspecified causes and a case of scarlet fever were reported.

Northwestern District

One infectious hepatitis and one diarrhoea and enteritis of the new born were reported.

Northern District

One case of poliomyelitis was reported. This was a two year old child, with date of onset in July — a Type III Polio virus was isolated. The child had received no polio vaccine. Also reported was one case of brucellosis and three cases of pertussis.

Winnipeg District

There were 44 cases of infectious hepatitis; 3 meningitis due to unspecified causes; 1 meningitis due to Coxsackie virus and 1 due to an ECHO virus. One case of epidemic encephalitis was reported. There were 9 cases of bacillary dysentery; 5 of food poisoning and 5 cases of scarlet fever. One case of paratyphoid fever was reported from the Children's Hospital. A report was received concerning 1 case of diphtheria in a sixty year old female.

Brandon District

Reports were received of nine cases of infectious hepatitis; two cases of meningitis due to unspecified causes; one bacillary dysentery; one diarrhoea and enteritis of the new born and one pertussis.

Central District

No reports were received.

Southern District

Reports were received on four cases of infectious hepatitis and two cases of scarlet fever.

NOW AVAILABLE

A SPECIALLY PREPARED FORMULA TESTED AND PROVEN BY THOUSANDS OF BABIES

● ● ● A proven formula for infant feeding, Pacific Partly Skimmed Milk is now available to the Prairie mother. Made to the same high standards of quality as Pacific Evaporated Milk, our partly skimmed milk has the following properties:

- **low butterfat content (2% when reconstituted with equal parts of water).**
- **increased Vitamin D (one pint contains 800 I.U.s).**
- **carefully controlled composition.**

Pacific Partly Skimmed is evaporated to double concentration, homogenized for increased digestibility, and sterilized in vacuum sealed, golden-lined tins.

- *Widely used in British Columbia under the Delta label where it has received the approval of B.C. doctors and mothers. This special formula was processed at the request of prominent pediatricians.*

You can recommend **PACIFIC PARTLY SKIMMED MILK** *with confidence*

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